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BRITISH HEART JOURNAL

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In association with the British Cardiac Society

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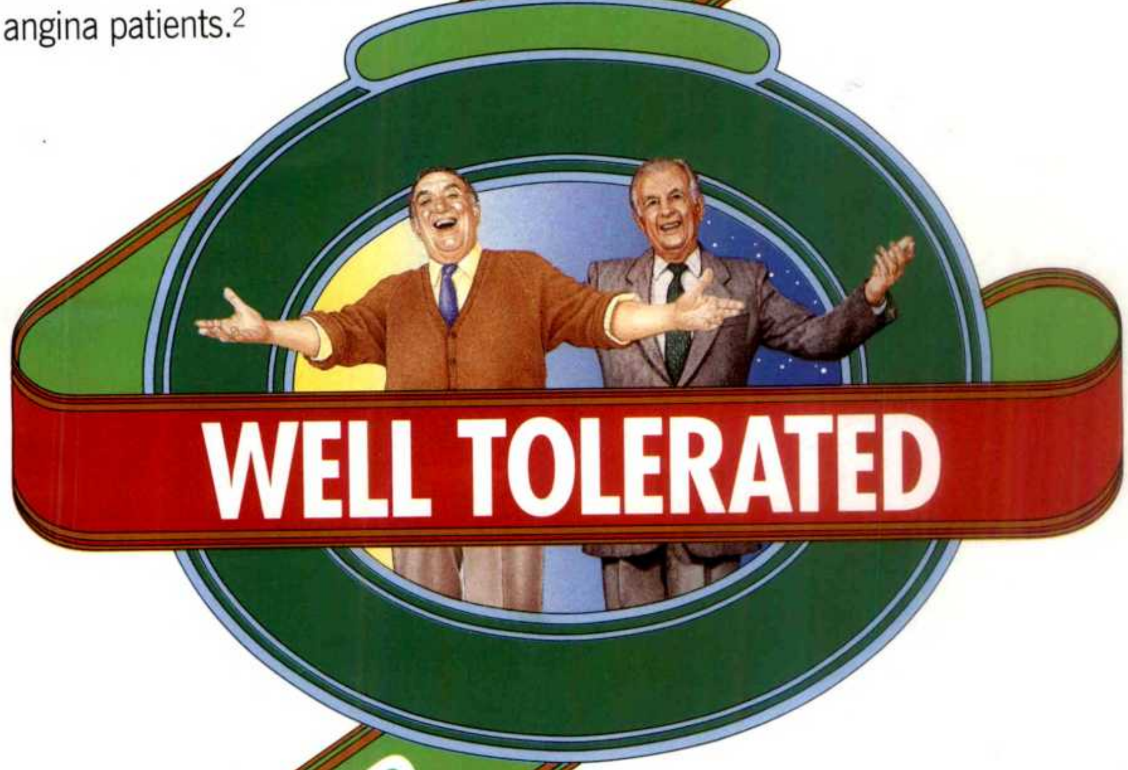

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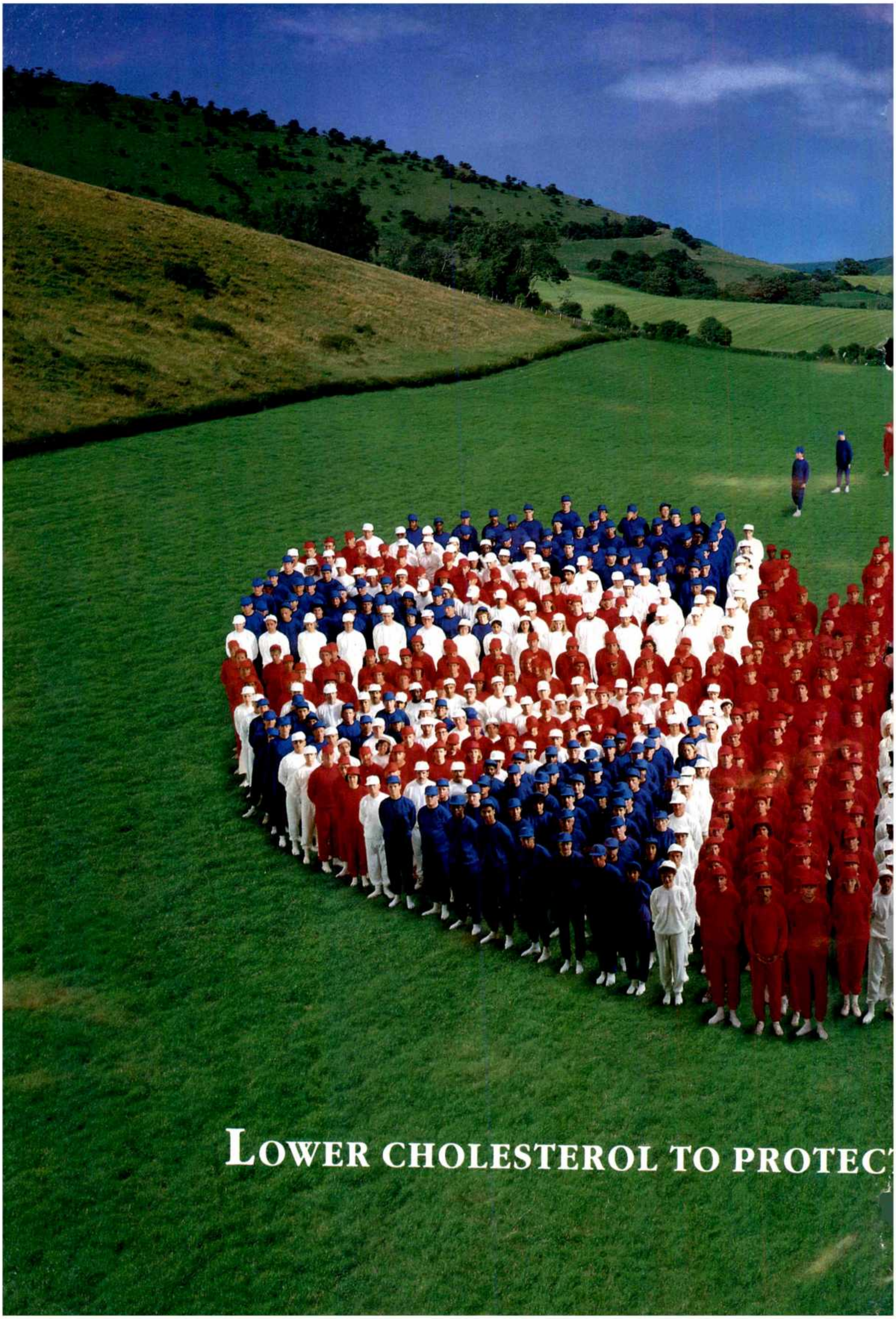
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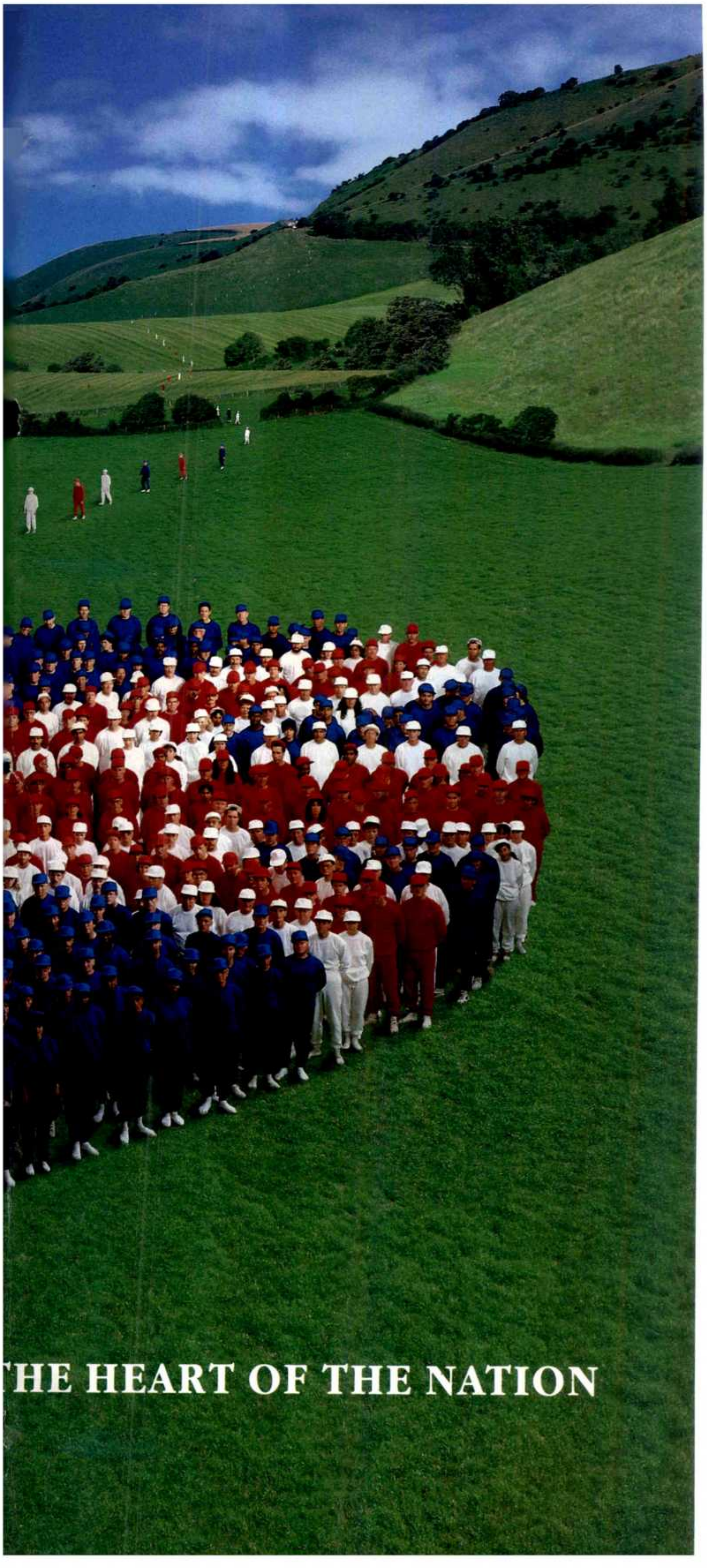
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Editorial

Understanding the nature of congenital division of the atrial chambers

Although the atriums must bow to the ventricles in terms of the power and complexity of the contractions of their muscular walls, morphologically they are far more complex than the mere forechambers implied by their classical name (defined in the *Shorter Oxford Dictionary* as "a portico in front of the principal doors of churches, etc".[1] The atriums are particularly important to those practitioners dealing with cardiology in the young, since recognition of their arrangement is the first step in the process of diagnosis now known generally as sequential segmental analysis.[2 3] In addition to recognising the disposition of the atriums relative to each other, however, the paediatric cardiologist must also recognise atrial malformations, no matter how rare or arcane they may be. It is a truism that recognition of such lesions is greatly enhanced when their morphology is understood.

This sets the scene for the discussion of hearts characterised by some degree of congenital partitioning within the morphologically left atrium. The reports collected in this issue of the *British Heart Journal* describe the use of colour flow mapping in diagnosis of division of the left atrium in association with congenitally corrected transposition;[4] diagnosis of a more classic case of divided left atrium by transoesophageal echocardiography;[5] and, perhaps most interestingly, a description of two cases with a prominent shelf guarding the entrance of the left pulmonary vein to the left atrium.[6] Although all the authors point to the rarity of such malformations, the April issue of *Pediatric Cardiology* too carries a report of a rare variant of divided left atrium,[7] as well as an account of the experience of Columbia University, New York, over a 28 year period, which encompassed 12 cases.[8] The importance of these lesions to all cardiologists is emphasised by the fact that both the patients from Boston[6] were adults referred for evaluation of a left atrial mass detected echocardiographically, while the patient studied at the Royal London Hospital was also an adult presenting with mitral stenosis in the third decade of life.[5] No longer, therefore, can adult cardiologists claim that such cases do not influence their practice. They may be rare but, as shown in these reports, they are readily recognised by cross sectional echocardiography and, providing their anatomy is understood they are easy to categorise and describe.

Unnecessary difficulties in description

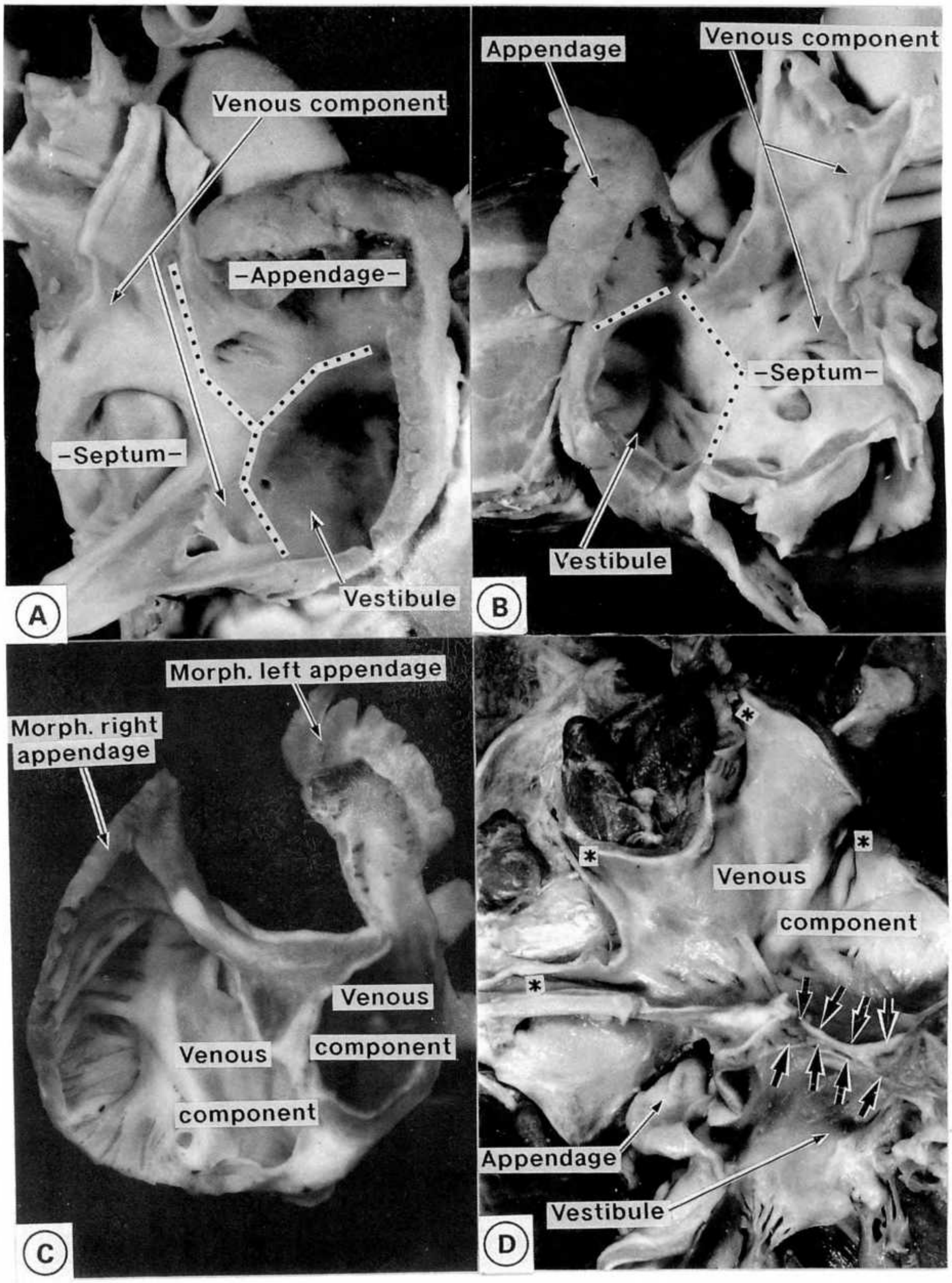
A review of the cases presented on pages 4, 6, and 9 of this issue along with those in *Pediatric Cardiology*,[7 8] shows that the popular term for description (and that almost universally adopted by the specialists) is "cor triatriatum sinister". The alternative offered by the Boston group is "remnant of the common pulmonary vein."[6] In their discussion, however, Manning and his colleagues[6] steer towards the more conventional "cor triatriatum", albeit giving an incorrect account of the developmental theory offered for the lesion by their cited embryologists.[9] More of the embryology later, but what of the description? What is "cor triatriatum sinister"? Anyone with the merest smattering of classical education (which is the most to which many of us can now lay claim) would interpret this to mean a heart with three left atriums! Is that what the term is meant to describe? Of course not. All the cases described show some degree of division of the left atrium. And it is known that the right atrium can similarly be congenitally divided. In my former years, I, too, was foolish enough to describe such a case as "cor triatriatum dexter".[10] But that was also when I wrote incomprehensible embryological dissertations[11] which, in retrospect, did little to enhance the understanding of congenital malformations.

I now believe we should describe these cases with simple English words, and, until we have strong evidence of the correct mechanics of cardiac development, we should eschew speculative embryology. Then if we look at previous accounts we see that "cor triatriatum sinister" is usually accompanied by a parenthetical English translation (subdivided left atrium.)[12 13] It is on the basis of division of the morphologically left atrium that the lesion is simply understood and, more importantly, correctly described.

Structure of the atriums

The atrial chambers have a comparable structure on the right and left sides of the normal heart, albeit with differences sufficiently distinct to permit their ready differentiation. On both sides the atriums possess a venous component, an appendage, and a vestibule. There is also a septum separating the atriums with characteristic features on its morphologically left and right sides. But the atrial septum can be totally lacking in morphologically abnormal hearts, producing a common atrium. The venous components of the atriums can also be totally deficient. It is the structure of the appendage, therefore, particularly the anatomy of its junction with the venous component of the atrium (fig 1C), that most readily permits the distinction of morphologically right and left atrial chambers.[14] It is usual during development of the morphologically right atrium for sheet-like valves to direct the richly oxygenated venous return from the inferior caval vein across the oval foramen to the left side of the heart and thence towards the developing brain. These valvar structures can remain unduly prominent in postnatal life,[15] and are then the anatomical substrate for division of the morphologically right atrium.[10]

Division of the morphologically left atrium takes a



These illustrations of normal human hearts show the features of (A) the morphologically (morph.) right and (B) the morphologically left atriums together with (C) the characteristic morphological differences between the two appendages based on the nature of their junctions with the venous components of the atriums. The heart shown in D is an example of the classic form of divided left atrium, with a prominent fibromuscular partition (between arrows) separating the pulmonary venous component from the rest of the left atrium. The asterisks show the four pulmonary veins. The lines on A and B are for the purposes of illustrating a concept—they do not demarcate obvious gross anatomical boundaries.

markedly different form. In this lesion, a fibromuscular partition is found between the venous component of the atrium and the remaining atrial components (fig 1D). This partition has no counterpart during normal development. It usually extends obliquely across the cavity of the atrium, and is most frequently positioned so that the oval fossa opens into the non-venous atrial component. The severity and timing of presentation is related to the size of the opening between the divided atrial components. The variety in position of the shelf, however, is legion. While association with other lesions permits truly mind-bending classifications to be assembled for the overall expression of the lesion.[13] My own preference is to describe simply the existence of the divided atrium and then list the associated lesions, particularly important confounding ones such as totally anomalous pulmonary venous connexion.[7]

Development of the lesion

Two of the reports in this issue offer embryological explanations of the lesions observed,[5 6] although the third, perhaps wisely, refrains from such speculations.[4] Conventional wisdom holds that the common pulmonary vein grows out from the developing atrium to make contact with the intrapulmonary venous plexus developing within the lung buds, and that subsequent incorporation of this venous plexus into the left atrium produces the typical arrangement of the left atrium with a pulmonary vein at each corner. Division of the left atrium is then explained either on the basis of malincorporation of the common pulmonary vein, or alternatively, as proposed by Van Praagh and Corsini,[9] its entrapment by the developing left sinus horn. As HL Mencken commented "there's always an easy solution to every human problem—neat, plausible and wrong".[16] The embryological hypotheses are based upon the study of serially sectioned human embryos—itself a very inexact science. Studies of graded animal models with immunocytological markers that distinguish the different developmental components will soon permit us to offer more exact accounts of atrial development. In the meantime, it seems imprudent to base concepts of abnormal hearts on such questionable premises. As the group from Riyadh point out[7] it is difficult to explain the coexistence of divided left atrium and totally anomalous pulmonary venous drainage on the basis of either theory.

Congenital heart disease made easy

In this issue of the *British Heart Journal* readers are confronted by four examples of rare congenitally malformed hearts. Two show the classic form of division of the left atrium. The other two show a previously undescribed (to my knowledge) variant in which a partition extends into the cavity of the left atrium between the openings of the left upper pulmonary vein and the left atrial appendage. This latter account is perhaps the most interesting. It is entirely reasonable to propose that this lesion is a minimal expression of the shelf that typically partitions the chamber in classically divided left atrium. The rapid advances presently being made in the study of cardiac development soon may permit us to make more accurate guesses at the nature of the dividing partition. In the meantime, it makes most sense to me to describe the cases in terms of division of the morphologically left atrium and to recognise that the fibromuscular shelf separates the pulmonary venous component from the remainder of the atrium.

ROBERT H ANDERSON

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Br Heart J 1992;68:4–5

CASE REPORTS: DIVIDED ATRIA

Remnant of the common pulmonary vein mistaken for a left atrial mass: clarification by transoesophageal echocardiography

Warren J Manning, Carol A Waksmonski, Marilyn F Riley

Abstract
Faulty incorporation of the common pulmonary vein leaves it as a distinct structure posteriorly, into which the pulmonary veins empty. This "chamber" is separated from the anterior "fetal" left atrium (containing the left atrial appendage and communicating with the mitral valve) by a diaphragm, and is known as cor triatriatum, one of the rarest of cardiac malformations. Less pronounced but still incomplete regression of this vein would result in the persistence of a portion of the common pulmonary vein appearing as a mass along the lateral wall of the left atrium at the junction of the left atrial appendage and left upper pulmonary vein. In two patients, both referred for evaluation of a left atrial mass, transoesophageal echocardiography identified the "mass" as a remnant of the common pulmonary vein.

Cardiologists need to be aware of this structural remnant and its possible variants so as to avoid misdiagnosis of this prominence as an atrial tumour or mass.

Transthoracic cross sectional echocardiography has revolutionised the antemortem examination of the heart for tumours and thrombi. Limitations of the transthoracic examination, however, include the dependence on transducer position and angulation[1] and the frequent inability to image adequately the left atrial appendage and pulmonary veins. More recently transoesophageal echocardiography has been shown to provide superior visualisation of the left atrium, left atrial appendage, and pulmonary veins.[2] We report the cases of two patients who were referred to our hospital for further evaluation of left atrial "tumours" identified by transthoracic echocardiographic study. In both instances, transoesophageal echocardiographic examination showed a prominent confluence of the left atrial appendage and left upper pulmonary vein.

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Case reports

CASE 1

A 60 year old white woman with a history of a remote myocardial infarction, mild aortic stenosis, and mild aortic insufficiency was admitted for evaluation of acute onset right-sided hemiparesis and dysarthria. A computed tomogram of the head without contrast was normal. Transthoracic echocardiography, to exclude a cardiac source of emboli, showed normal chamber sizes and left ventricular systolic function. An elongated left atrial mass was noted originating at the base of the left atrial appendage (fig 1A). She was transferred for further evaluation. Transoesophageal echocardiography showed normal chamber sizes with a prominent confluence of the left atrial appendage and left upper pulmonary vein extending 2·5 cm into the body of the left

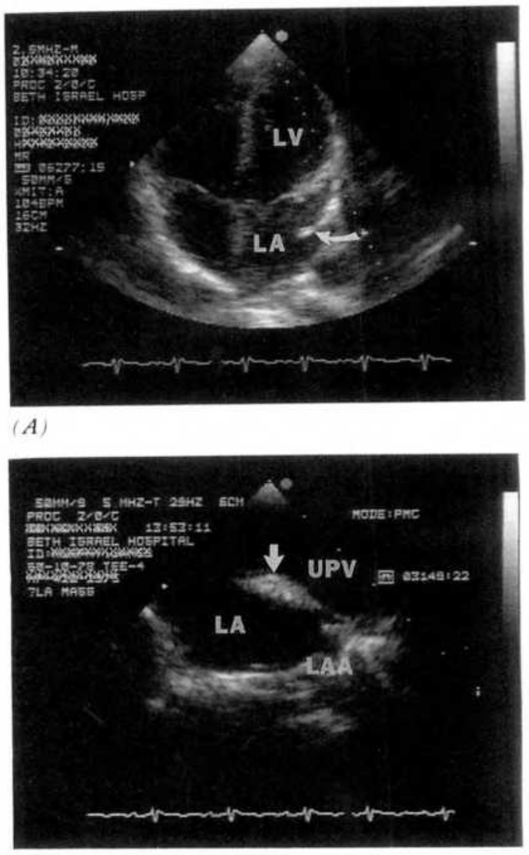

Figure 1 (A) Apical four chamber view showing an elongated echodensity/mass (arrow) originating near the base of the left atrial appendage. LA, left atrium; LV, left ventricle. (B) Transoesophageal study of the patient shown in (A), showing prominence (arrow) of the confluence of the left atrial appendage (LAA) and left upper pulmonary vein (UPV).

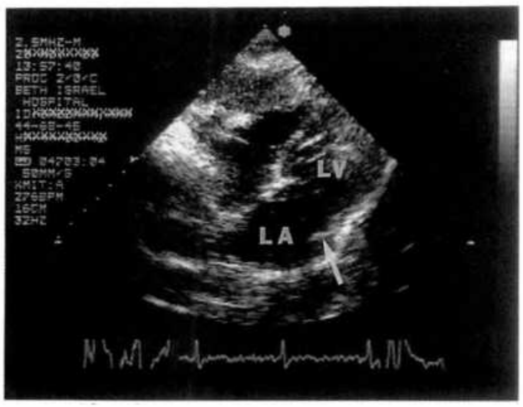

Figure 2 Apical four chamber view showing left atrial enlargement and a linear echodensity/mass along the lateral wall (arrow) of the left atrium.

atrium (fig 1B). No evidence of an intracardiac mass was seen.

CASE 2

A 67 year old white man was well until his vision became blurred a week before admission. Physical examination showed isolated hemianopsia and was otherwise normal. A computed tomogram of the head showed an occipital infarct. Transthoracic echocardiography, performed to exclude a cardiac source of emboli, showed mild left atrial enlargement and a left atrial mass (fig 2). He was referred for further evaluation. transoesophageal echocardiography was performed to define better the abnormality visualised by transthoracic study. It showed an enlarged left atrium with a prominent confluence of the left atrial appendage and left upper pulmonary vein. No evidence of tumour, thrombus, or other mass was seen.

Discussion

Primary intracardiac tumours are rare: they account for less than 0·3% of all tumours identified at necropsy.[3] Most intracardiac tumours are myxomas, of which most arise from the left atrium, with lipomas, papillary fibroelastomas, angiosarcomas, rhabdomyomas, and fibromas being increasingly less common.[3] Antemortem diagnosis of intracardiac tumours has become common with the development of cardiac ultrasound. Transthoracic cross sectional echocardiography has revolutionised the examination of the heart for tumours and thrombi, because it shows the spatial orientation and accurately defines the location, size, shape, and site of attachment of intracardiac tumours.[4]

The pulmonary veins develop as a posterior protrusion from that portion of the embryonic heart destined to become the left atrium.[5] This protrusion, the common pulmonary vein, is a temporary structure that communicates with the splanchnic plexus to establish pulmonary venous drainage to the left atrium.

During the fifth embryonic week the common pulmonary vein vanishes as it becomes incorporated in the left atrium proper.[5] Normal incorporation results in each pulmonary vein joining the left atrium separately and directly. Faulty incorporation leaves the common pulmonary vein as a distinct structure posteriorly, into which the pulmonary veins empty. This "chamber" is separated from the anterior "fetal" left atrium (containing the left atrial appendage and communicating with the mitral valve) by a diaphragm. This condition, known as cor triatriatum, is one of the rarest of cardiac malformations.[6] This dividing membrane lies horizontally above the level of the atrial appendage and is composed of cardiac muscle covered on its superior and inferior aspects by endocardial tissue.[5]

Cor triatriatum results if there is minimal incorporation of the common pulmonary vein. We believe the abnormality noted on transthoracic exam in these two cases, and identified by transoesophageal study as a prominence at the junction of the left upper pulmonary vein and left atrial appendage, was caused by incomplete incorporation of this membrane into the left atrium. This suggests a continuum between "normal" incorporation of the main pulmonary vein and the syndrome of cor triatriatum. Cardiologists need to be aware of this structure and its possible variants so as to avoid misdiagnosis of this prominence as an atrial tumour or mass.

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A characteristic continuous wave Doppler signal in cor triatriatum?

M Alwi, Z A A Hamid, R Zambahari

Abstract

Continuous wave Doppler recordings of the turbulent jet through the restrictive orifice of a left atrial partition in a patient with corrected transposition of the great arteries and cor triatriatum showed alternate bands of high intensity diastolic and low intensity systolic signals with preservation of the normal configuration of the diastolic E and A peaks. It is thought that Doppler studies in cor triatriatum will provide useful complementary haemodynamic information in the echocardiographic diagnosis of this anomaly.

Cor triatriatum can be diagnosed by cross sectional echocardiography. Because this is a rare condition there are few reports of the diagnosis of cor triatriatum by Doppler echocardiography. We report a case of congenitally corrected transposition of the great arteries with cor triatriatum and an unusual continuous wave Doppler signal from the turbulent flow through the orifice of the left atrial partition.

Case report

A four year old boy who had been treated for asthma was referred because of a heart murmur. He had mild exercise intolerance. On clinical examination he was comfortable at rest and there was no cyanosis. His pulse rate was 105 beats/min. There was a precordial bulge and grade 3/6 systolic and diastolic murmurs were heard over the apex. The chest radiograph showed situs solitus, levocardia, and mild cardiomegaly. The appearance of the lung fields was suggestive of pulmonary venous obstruction with perihilar congestion and fluid in the horizontal fissure. The electrocardiogram showed sinus rhythm, an axis of − 20°, and left atrial enlargement. Cross sectional, colour flow mapping and continuous wave Doppler examination was performed with a Toshiba SSH-160A. The descending aorta, inferior caval vein, and abdominal viscera were normally lateralised. There were atrioventricular and ventriculoarterial discordant connections without an associated ventricular septal defect, pulmonary stenosis, or tricuspid regurgitation. The peak pulmonary velocity was 1·4 m/s. The pulmonary arteries were dilated. Additionally, a partitioning membrane in the left atrium was seen and distended pulmonary veins entered the prox-

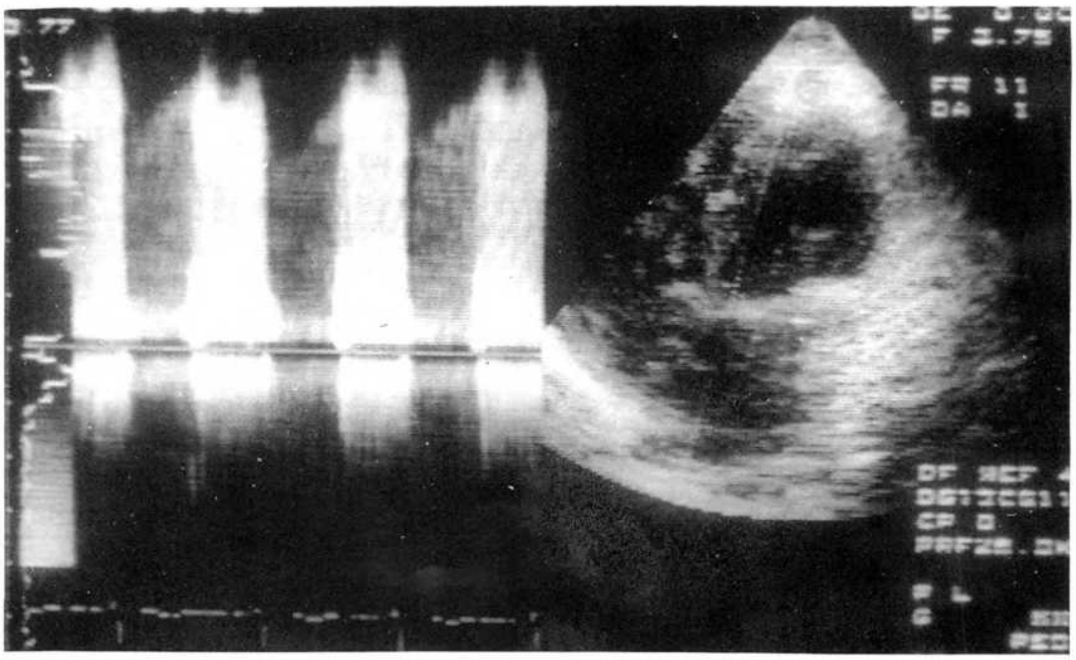

Figure 1 Continuous wave Doppler signal of flow through the membrane orifice showing alternate bands of high intensity diastolic and low intensity systolic signals with normal E and A peaks. Peak velocities were high in both parts of the cardiac cycle (upper limit of velocity scale is + 3·77 m/s).

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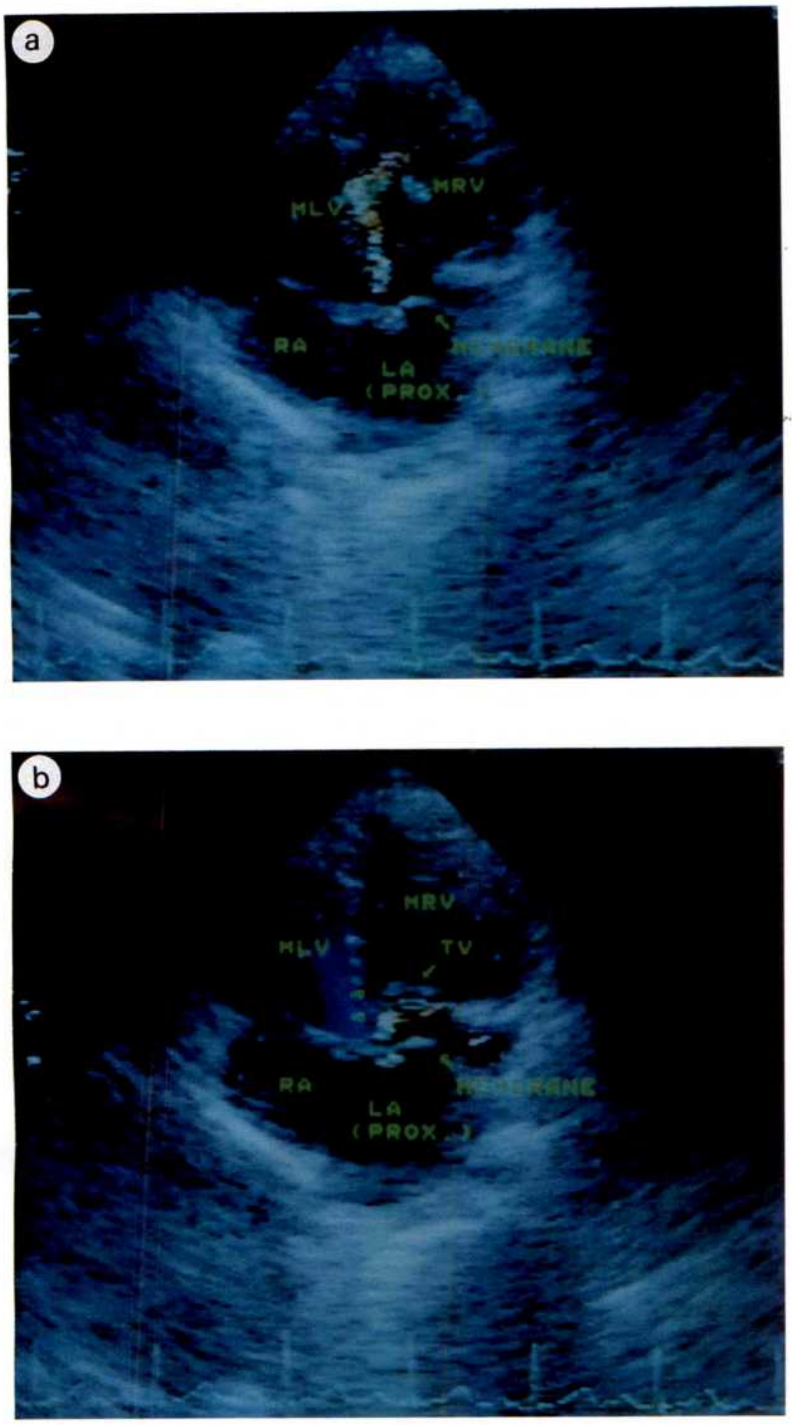

Figure 2 Colour flow mapping showing (A) the diastolic frame with a turbulent jet through the restrictive membrane orifice and (B) the systolic frame showing attenuated flow through the orifice against a closed atrioventricular valve. Note the more apical setting of the atrioventricular (morphologically tricuspid) valve (double arrows). LA (prox), proximal left atrial chamber; MRV, morphologically right ventricle; MLV, morphologically left ventricle; RA, right atrium; TV, tricuspid valve.

imal chamber. This membrane was attached some distance away from the annulus of the atrioventricular valve. Colour flow mapping showed a turbulent jet arising from a very small eccentric orifice in the partitioning membrane close to the interatrial septum.

Continuous wave Doppler interrogation of the turbulent jet through the orifice showed an unusual spectral display. There were alternate bands of high intensity diastolic and low intensity systolic signals in a positive direction producing a vertically striped appearance. The peak velocities were abnormally high in both parts of the cardiac cycle. The velocity of the low intensity systolic signals reached a minimum (1·8 m/s) in early systole and gradually peaked (2·4 m/s) at end systole (a mean of three consecutive beats). In the high intensity diastolic signals the normal E and A peaks were preserved despite a high peak velocity of 2·8 m/s. The passive phase of ventricular filling in diastole was not prolonged (fig 1).

We compared flows through the membrane orifice in both parts of the cardiac cycle on colour flow mapping by means of the cine-loop facility and electrocardiographic marker to identify systolic and diastolic frames. Continued forward flow through the orifice, though attenuated, was seen during systole (fig 2). The diagnosis was confirmed at surgery and the membrane was excised. Postoperatively the spectral display of flow through the left atrioventricular valve was normal, resembling that of the right atrioventricular valve.

Discussion

Though the coexistence of cor triatriatum with corrected transposition of the great arteries is rare it has been reported before.[1] Because cor triatriatum can be readily diagnosed by cross sectional echocardiography cardiac catheterisation is not usually needed before operation.[2]

Because the orifice in the partitioning membrane is usually very small and restrictive of flow, Doppler echocardiography was expected to provide haemodynamic information that complemented the anatomical details obtained by cross sectional echocardiography. However, there are few reports on this subject because the condition is so rare. Previous reports in English merely mentioned high velocity diastolic signals when the pulsed Doppler sample volume was placed beneath the restrictive orifice.[3 4]

Several of the features of the signals recorded in our patient during continuous wave Doppler examination had not been described before. Firstly, by using the cine-loop facility and analysing the colour flow images frame by frame we were able to demonstrate continued forward flow through the orifice of the membrane during the phase when the morphologically tricuspid (left atrioventricular) valve was closed in systole. We suggest that this was the mechanism responsible for the low intensity positive signals on the spectral display: pressure in the distal left atrial chamber would be expected to remain lower than that in the proximal chamber and hence cause a continuous forward flow. These positive systolic signals have been described before in a report in Spanish.[5] Secondly, despite the high velocity in diastole, the E and A peaks were normal, suggesting normal mid-diastolic closure of the atrioventricular valve with no prolongation of the phase of passive ventricular filling and that the obstruction is not likely to be at the level of the valve. These spectral display findings were not seen in severe obstruction of the left ventricular inflow tract by a stenotic mitral valve.[6] Supravalvar mitral rings may pathophysiologically mimic cor triatriatum but they seldom occur in isolation and are commonly associated with congenital mitral stenosis.[7] We do not know of any reports of Doppler examination in congenital mitral stenosis but, as in acquired mitral stenosis, we would not expect a positive systolic signal on the spectral display because the pressures in the left ventricle and left atrium would prevent forward flow through the mitral valve during systole. It remains to be seen whether the features we describe are characteristic of cor triatriatum.

We thank Mrs Zahiyah Bte Abdul Rahman and Mr Kamaruzaman Bin Othman.

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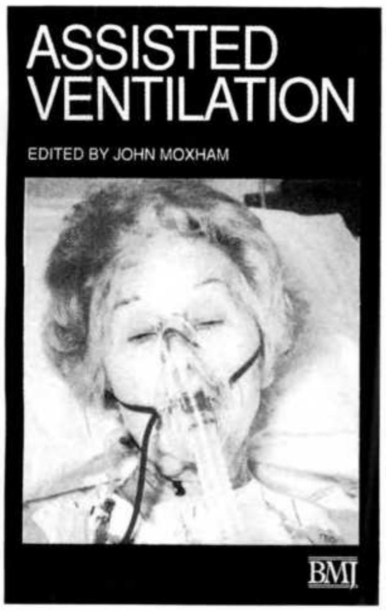

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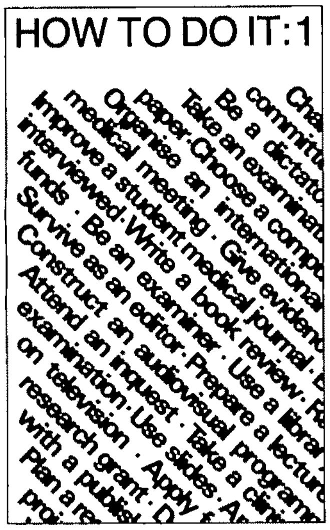

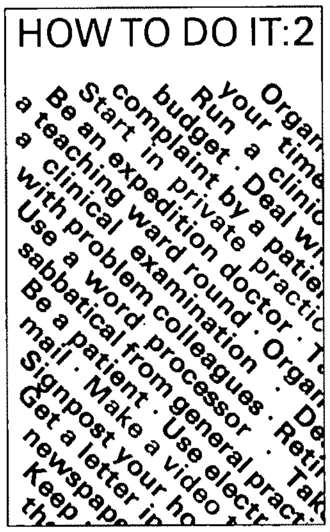

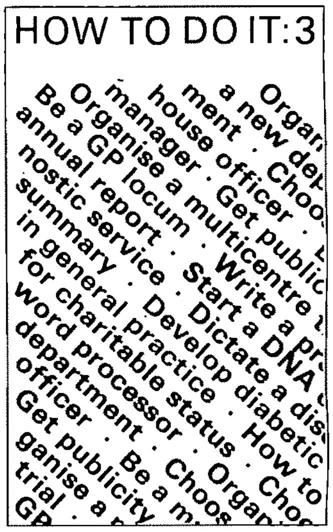

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Cor triatriatum sinister, not mitral stenosis, in an adult with previous Sydenham's chorea: diagnosis and preoperative assessment by cross sectional echocardiography

Mark A de Belder, Vincenzo Argano, Christopher J Burrell

Abstract

In cor triatriatum sinister, one of the rarest congenital cardiac anomalies, a membrane divides the left atrium into a pulmonary venous component above and the vestibule below. The importance of the anomaly lies in the effects of the resultant pulmonary venous obstruction that usually present in the first year of life and can mimic obstructed total anomalous venous drainage or congenital mitral stenosis. A case presented as mitral stenosis in the third decade of life, ten years after a well documented episode of Sydenham's chorea. The diagnosis was made rapidly by transthoracic echocardiography and transoesophageal echocardiography was used for complete assessment. Cardiac catheterisation added nothing to the non-invasive diagnosis or the preoperative assessment. Uncomplicated corrective surgery was undertaken.

Cor triatriatum sinister is a rare cardiac anomaly in which the left atrium is divided into upper and lower chambers by a transverse membrane. Communication between the upper and lower chambers is via a stenotic fenestration in the membrane which tends to lead to a rise in pulmonary venous pressure. The upper chamber usually communicates with the right atrium via a patent foramen ovale or atrial septal defect so that the clinical features may simulate anomalous pulmonary venous connection. Less frequently the foramen ovale communicates with the distal chamber so that the clinical features mimic mitral stenosis.

The diagnosis of rheumatic mitral stenosis is now rare in the white population with the great decline in the incidence of rheumatic fever. We report the case of a young man presenting ten years after an episode of typical Sydenham's chorea with atrial fibrillation and left atrial enlargement that initially was thought to be due to rheumatic mitral stenosis.

Case report

A 22 year old white man who participated in the strenuous pastime of mediaeval jousting presented with exertional breathlessness. Ten years earlier he had consulted a neurologist with choreiform movement associated with facial grimacing so typical of Sydenham's chorea that he agreed to be admitted for the benefit of the medical students and his case was later presented locally (West Country Physicians Meeting, 1983).

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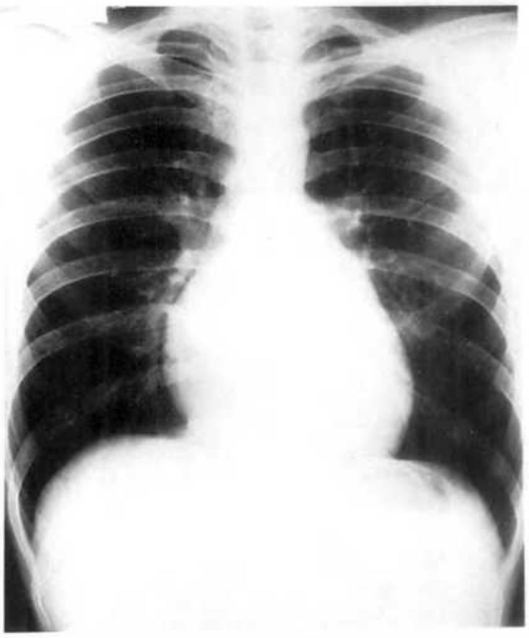

Figure 1 Chest radiograph in posteroanterior projection showing left atrial enlargement.

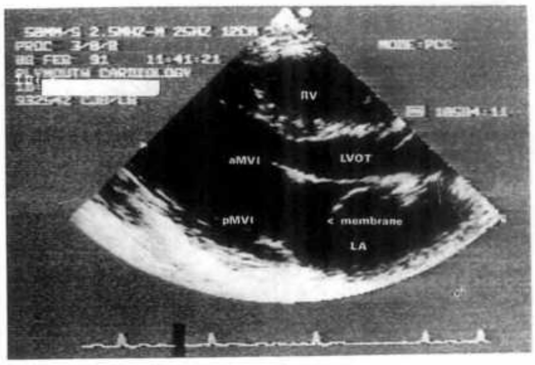

Figure 2 Cross sectional transthoracic echocardiogram (parasternal long axis view), showing an enlarged left atrium subdivided by a fibromuscular membrane (arrowed). LA, left atrium; LVOT, left ventricular outflow tract, aMVl, anterior mitral valve leaflet; pMVl, posterior mitral valve leaflet; RV, right ventricle.

Preliminary investigation showed him to be in atrial fibrillation with radiographic evidence of left atrial enlargement (fig 1), though it was noted that the left atrial appendage seemed normal. At auscultation a loud first heart sound and a variable diastolic murmur was heard, leading to the provisional diagnosis of rheumatic mitral stenosis. However, transthoracic echocardiography showed a normal mitral valve with a fibrous membrane dividing the left atrium into upper and lower chambers (cor triatriatum sinister) (fig 2).

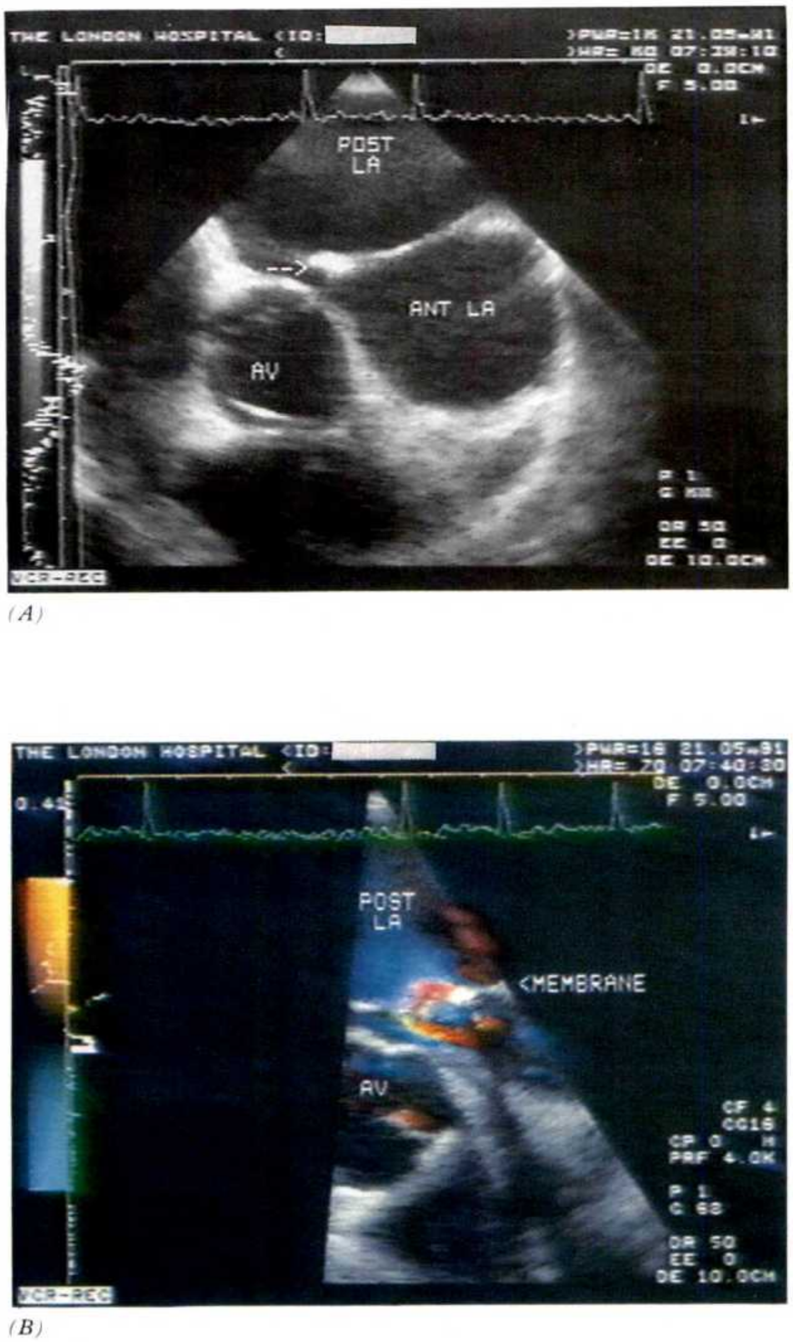

Figure 3 Cross sectional transoesophageal echocardiograms. (A) Horizontal section at the level of the aortic valve (AV) just below the level of the left atrial appendage. A defect (arrowed) is seen towards the medial side of the membrane, adjacent to the aortic root. Just below this level the membrane continued posteriorly and was attached to the posterior aspect of the atrial septum. AV, aortic valve; POST LA, posterior chamber of left atrium; ANT LA, anterior chamber of left atrium. (B) Colour flow map at the same level as 3A. There was a zone of flow acceleration in the posterior chamber, shown by serial colour aliasing, leading to a jet that passed through the defect in the membrane (arrowed) towards the mitral valve. AV, aortic valve; POST LA, posterior chamber of left atrium.

Cross sectional transoesophageal echocardiography showed the anatomy in detail (fig 3A). There was a small defect with a calcified rim on the medial side of the membrane adjacent to the wall of the aortic root. The pulmonary veins all drained into the upper chamber and colour flow doppler showed a high velocity jet from the upper chamber through the defect towards the mitral valve (fig 3B). The diagnosis and absence of associated cardiac abnormalities were confirmed by biplane cardiac angiography of the right and left heart (with a late phase pulmonary angiogram). Saturations were normal and pressures were recorded as follows (mm Hg): pulmonary artery 35/14, pulmonary capillary wedge 12 (mean), left ventricle 140/0-2.

At operation via a median sternotomy, hypothermic cardiopulmonary bypass was established and an incision was made in the left atrium at the Sondergaard sulcus, just posterior to the interatrial groove. The findings exactly matched the echocardiographic appearances. There was a thin fibromuscular septum subdividing the left atrium. It had an oval orifice (1 cm diameter) with calcified margins between the large upper and smaller lower chambers. The pulmonary veins drained separately into the upper chamber with which the foramen ovale also communicated. There was no atrial septal defect and no thrombus was present. The membrane was excised completely via the fenestration and though the mitral orifice was quite large, the valve apparatus was normal and shown to be competent. The left atrium was closed and the heart was defibrillated into sinus rhythm. The postoperative course was uncomplicated.

Three months later he was symptom free, and in sinus rhythm; he had not returned to mediaeval jousting. He had had a recurrence of chorea and his previous medication had been restarted.

Discussion

Cor triatriatum sinister accounts for only 0·1% of all congenital cardiac anomalies. The anomaly, first described in 1868,[1] about two hundred years after Thomas Sydenham's description of childhood chorea, consists of an abnormal fibromuscular membrane dividing the left atrium into upper and lower chambers. There are two main variants depending on the position of the foramen ovale in relation to the membrane. When the upper chamber communicates via a patent foramen ovale (or an atrial septal defect) with the right atrium, obstructed total anomalous pulmonary venous drainage may be mistakenly diagnosed. When there is communication between the lower chamber and the right atrium cor triatriatum can mimic mitral stenosis.

In normal embryological development the common pulmonary vein originates between the fifth and eighth weeks of life as a midline structure below the septum primum. The normal distal connection of the pulmonary veins results from the incorporation of this structure into the left atrium. The embryological basis for the anomaly remains uncertain but it may be due to a failure of incorporation, an overgrowth of the septum primum, entrapment of the common pulmonary vein, or indeed a combination of these.[2-4]

Diagnosis, with evidence of increased pulmonary venous pressure, is most commonly made in the first year of life; our patient did not present until he was 22, perhaps because the fenestration in the anomalous membrane was larger than usual (1 cm diameter). Fenestrations can be as small as 1 to 2 mm in diameter. Associated congenital cardiac abnormalities are common, particularly atrial septal defect and true anomalous pulmonary venous drainage;[5 6] a persistent left superior vena cava has also been observed quite frequently.[6 7]

In the past, accurate preoperative elucidation of the anatomy has depended upon left and right heart catheterisation with pulmonary angiography to show the membrane during the late phase in the right anterior oblique projection. Recent advances in echocardiographic techniques and particularly the application of transoesophageal echocardiography, however, allowed us to make complete preoperative assessment non-invasively; cardiac catheterisation did not contribute additional information.

Surgical treatment consists of excision of the fibromuscular membrane. The surgical approach is made directly into the upper chamber of the left atrium or, in smaller patients, via the right atrium, particularly if there is an associated atrial septal defect. However, this approach can make closure of the patent foramen ovale or repair of the atrial septal defect difficult and the mitral valve apparatus may be damaged. In infancy, surgical correction of isolated cor triatriatum can be associated with a high mortality (up to 40%) but long term results after successful correction are usually excellent.[5 6]

Rheumatic fever is now rare, so the diagnosis of Sydenham's chorea in this patient was in itself of interest. The association between this condition and a congenital abnormality that may mimic mitral stenosis was presumably a chance one. We are not aware of any association between cor triatriatum sinister and choreiform movement.

We thank Mr C T Lewis for his help and expertise in the management of this patient and Mr D J Morris and Mrs F Roach (Derriford Hospital, Plymouth) for their assistance.

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REVIEW

Assessment of right ventricular function and its role in clinical practice

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Far more has been published on left ventricular function than on right ventricular function in both congenital and acquired heart disease. Lately, however, more attention has been directed towards right ventricular performance and the problem of right ventricular dysfunction and the imbalance is now being redressed. This is in part related to improved investigative techniques, but it is also coupled to heightened awareness of the functional relevance of the right ventricle in maintaining the circulation. For example it has now been shown that there is significant impairment of right ventricular performance, with pathophysiological consequences for the circulation, in a range of conditions including acute[1–3] and chronic[4–6] coronary arterial disease, valvar heart disease,[6] and septicaemic shock.[7 8] In addition, right ventricular dysfunction influences survival in patients with acute[9] and chronic[10] left ventricular injury and in patients with congenital heart disease both before and after surgical intervention.[11–13]

Why has right ventricular function been ignored until recently?

The right ventricle has been neglected for many reasons, but the chief one is the difficulty of accurately assessing right ventricular size and function, primarily because of its complex shape. Modern imaging techniques, however, have now largely overcome this problem. An important contributory factor though has been the widely held view that the right ventricle is almost unnecessary to the circulation and that attention should be focused on the more important left ventricle. Early experimental studies[14–16] that showed that extensive damage to the right ventricular free wall caused little haemodynamic upset led to the conclusion that the right ventricle was essentially a passive conduit between the systemic veins and the pulmonary artery. Further support for this idea came from the prolonged survival of patients with little or no right ventricular functional contribution (for example, patients with pulmonary pulmonary atresia and intact interventricular septum or tricuspid atresia) and from the success of surgical procedures, such as the Fontan operation, that exclude the right ventricle from the circulation.[17] Later, more sophisticated animal experiments suggested that this concept was incorrect. When the right ventricular free wall, either alone[18] or in combination with the interventricular septum,[19] was replaced by non-contractile material the degree of haemodynamic upset was great, and most animals died within hours of operation.

Evaluation of right ventricular size and function

Three aspects of right ventricular anatomy make it difficult to assess function: (*a*) Left ventricular volume can be calculated by simple mathematics and a single plane angiogram but the more complex shape of the right ventricle demands orthogonal biplane pictures and computer analysis of the data; (*b*) heavy trabeculation of the right ventricular free wall complicates edge recognition; (*c*) with some imaging techniques an overlap between the right ventricle and other cardiac chambers makes it difficult to measure volume reliably.

Contrast ventriculography, echocardiography, and radionuclide ventriculography have largely overcome these problems and all have been used to analyse right ventricular volume and function. More recently, use of rapid computed tomography and gated magnetic resonance imaging has improved image resolution.

CONTRAST VENTRICULOGRAPHY

Contrast ventriculography was the first method used to visualise the right ventricular chamber and it remains the reference standard for volumetric or function measurements.

Reedy and Chapman were the first to attempt right ventricular volume measurement from biplane angiograms;[20] they adopted the novel approach of measuring the combined volume of right and left ventricles from simultaneous right and left ventriculograms by using a multiple slice technique and then subtracting the volume of the left ventricle and septum to estimate the volume of the right ventricle. Because of the practical difficulties inherent in simultaneous right and left ventriculography this method was never widely used to measure human right ventricular volume. However, the general principle put forward by Reedy and Chapman of using multiple slices to measure the volume of complex shapes has been adopted as the best method for measurement of right ventricular volume. Multiple slice methods rely on dividing the ventricle into a series of equal parallel slices of known thickness. The cross sectional shape of each slice is assumed to be an ellipsoid or rectangle, the lengths of the major and minor axes of which are derived from simultaneous orthogonal angiograms. By the application of Simpson's rule the total volume can be derived from the sum of the volumes of each slice.[21] One error inherent in this method is that the cross sectional shape of the normal right ventricle may no longer be ellipsoidal if haemodynamics function is abnormal.[22] Another potential source of error relates to the number of slices into which the ventricle is divided. Methods that use a fixed slice depth of say 0·5 cm may divide the right ventricle into as few as four or five slices when it is small, and there is some evidence that about 40 slices are required for accurate volume assessment.[23] In addition, any multiple slice method is laborious and time consuming even with computerised analysis. Because of this much effort has gone into attempts to produce an accurate but simpler method to measure right ventricular volume. Most of these methods assume the right ventricle to be a simple geometric shape—for example, a triangular based prism,[24] or a triangular based pyramid[25]—or use a two-chamber technique[26] that divides the right ventricle into the body (the volume of which is derived from one of the geometric models above) and outflow tract (which is assumed to have the volume of a cylinder). These techniques are simpler to apply and almost as accurate as applying Simpson's rule in the estimation of the volume of normal right ventricular casts from humans and animals, but they are less reliable when the shape of the right ventricle is abnormal.[24]

With either technique right ventricular volume can now be measured from biplane angiograms as accurately as left ventricular volume and angiographic right ventricular volume and ejection fraction measurements have now been used to assess right ventricular function in a wide range of congenital and acquired heart disease.

ECHOCARDIOGRAPHY

The complex shape of the right ventricle makes assessment of its function difficult whichever method is used but in addition the position of the normal right ventricle directly beneath the sternum poses specific problems for echocardiography. These problems are compounded by chronic lung disease and previous thoracic surgery, which are common in patients in whom right ventricular function studies are often crucial. Despite these limitations, right ventricular size and function are increasingly estimated by M mode and cross sectional echocardiography.

The earliest attempts to evaluate right ventricular function by M mode echocardiography[27 28] were limited by the difficulty in delineating the endocardial surfaces and dependence on the correct orientation of the ultrasound beam across the cavity. Cross sectional echocardiography overcame some of the problems of beam orientation[29] by using anatomical landmarks to standardise the orientation of the ultrasound beam within the right ventricular cavity. This approach gives acceptable measurements of right ventricular volume and function.

RADIONUCLIDE VENTRICULOGRAPHY

Right ventricular function has been assessed by first pass and equilibrium techniques. The first pass technique has the advantage of rapid data acquisition but assumes homogeneous mixing of the tracer—an assumption that is perhaps optimistic.[30] Even if complete mixing of the tracer is assumed, there are other potential problems, particularly separation of the right ventricular image from that of the right atrium, pulmonary arteries, and left ventricle. Sophisticated programs for boundary definition and for background subtraction in more modern equipment have gone some way to minimise this error but it can never be eliminated.[31]

Equilibrium studies use counts recorded during successive beats over 10–15 minutes and are analysed by electrocardiographic gating. The cardiac cycle is divided into a series of 50 ms frames, and frames can be displayed sequentially to measure ejection fraction or to produce a moving image of an "average" cycle in order to examine wall motion. The problems associated with gated blood pool imaging are those common to all radionuclide techniques—that is, border recognition, chamber overlap, etc—but these are even more pronounced in equilibrium studies because radioactivity is emitted from all structures containing blood. It is therefore important to select views of the right ventricle to optimise the separation from surrounding structures.

The importance of the above factors is illustrated by the wide variation in reports of right ventricular ejection fraction measured by different radionuclide techniques; the mean (SD) "normal" right ventricular ejection fraction varies between 23 (12)%[32] and 60 (7)%.[33]

CONCEPTS OF RIGHT VENTRICULAR FUNCTION ASSESSMENT

Right ventricular systolic and diastolic function can be assessed with some validity by various imaging techniques and calculation methods. As a result function—expressed as a simple index such as ejection fraction—can be easily assessed. The evaluation of right ventricular performance, however, demands an understanding of the interplay between the right ventricle and the rest of the circulation. Like the left ventricle, the function of the right ventricle is modified by the contractile state of the myocardium (contractility); preload; afterload; and to some extent the more minor effects of intrapericardial pressure, left ventricular contractile performance, and the contribution to right ventricular work of the septum. Any analysis of right ventricular performance must therefore take into account this relation between intrinsic and extrinsic factors. Variables such as ejection fraction may not be sufficiently sensitive to evaluate "intrinsic" right ventricular contractile performance even although it seems to change appropriately in disease states such as acute inferior infarction,[34] obstructive airways disease,[35] and left-sided heart lesions.[36] Certainly the right ventricular ejection fraction is sensitive not only to changes in contractility but also to changes in preload and afterload. It is therefore tempting to study other indices of right ventricular function such as end diastolic and end systolic volume and right ventricular pressure volume relations. Though individual absolute volume measurements are known to be less accurate than estimates of ejection fraction, in many cases they may give a better indication of right ventricular function. For example, right ventricular end systolic volume is dependent mainly on afterload and contractility but not on preload; and in circumstances such as right ventricular volume overload the end systolic volume may be a more useful indicator of contractile state than the ejection fraction.

Construction of right ventricular pressure volume loops may also permit better evaluation of right ventricular function. The study of phase relations between pressure and volume have greatly increased knowledge of left ventricular function, enabling evaluation of (*a*) phase relations of pressure and volume in the normal and diseased ventricle,[37] (*b*) the energetics of contraction,[38](*c*) the cycle efficiency of ventricular function,[39] and (*d*) the establishment of an end systolic pressure volume relation[40] that, although controversial, is commonly used as a load independent measure of contractility. In view of the possible physiological and diagnostic information that can be derived from pressure volume relations, it is suprising how little attention has been paid to the human right ventricular pressure volume relation. In 1984 Friedman *et al* used an equilibrium radionuclide method for right ventricular volume measurements with "simultaneous micromanometer pressure measurements".[41] Unfortunately there were several major weaknesses in this study, particularly in relation to the accurate timing of events. In 1988 Redington *et al* studied and described the normal right ventricular pressure volume relations by recording biplane right angiograms and simultaneous high fidelity pressure recordings[42] and subsequently reported the changes in this relation that were associated with pressure and volume overload.[43] The construction of such loops is of great potential clinical significance because they provide an insight into right ventricular function when used in the detailed assessment of patients with right heart disease.

Clinical importance of the assessment of right ventricular function

It is clear that an accurate measure of right ventricular function is vital in the management of patients with a wide variety of clinical problems, both to plan treatment and to predict prognosis.

The development of right ventricular dysfunction with myocardial infarction is now recognised as a common occurrence. With anterior myocardial infarction there is usually persistent left ventricular regional impairment and transient global right ventricular impairment, whereas in inferior infarction there is often persistent regional impairment of both the right and left ventricles.[1] The haemodynamic response of the two ventricles to infarction differs, and in patients with extensive right ventricular infarction the development of cardiogenic shock is not uncommon[44,45] and requires a different therapeutic approach.[44,46] The degree of right ventricular dysfunction can also be used to assess prognosis. Polak *et al* studied patients with a reduced left ventricular ejection fraction and clinically evident heart failure secondary to coronary artery disease.[10] Those patients surviving two years into the study had a higher right ventricular ejection fraction and less extensive left ventricular dyskinesis. Two year mortality was significantly higher in patients with a lower right ventricular ejection fraction ($< 35\%$) and right ventricular ejection fraction was the single most useful indicator of patient outcome overall.

Right ventricular function is also important in predicting the outcome in patients with ventricular septal defects after myocardial infarction. In a small study of patients with acute ventricular septal defect requiring intra-aortic balloon pumping and open heart surgery Grose *et al* described right ventricular dysfunction as the major cause of death in 25% of cases and a major contributory factor in a further 37% of cases.[6] In a larger study Radford *et al* followed the course of 41 patients with post-infarction ventricular septal defect.[47] Cardiogenic shock developed in 55% of their patients and this was unrelated to the site of infarction, the extent of coronary artery disease, the left ventricular ejection fraction, or the pulmonary systemic flow ratio. The mean pulmonary artery pressure, however, was lower in the patients with shock than those without, suggesting that right ventricular impairment was a contributory factor to shock. Survival was better in those patients without shock and with essentially normal right ventricular function, but was not related to the extent of coronary artery disease, left ventricular function, or the size of the left to right shunt.

Right ventricular dysfunction is also common in other shock-like states including septicaemic shock[7,8] and post-cardiotomy shock,[9] probably as a result of alterations in right ventricular afterload and contractility.[8] This is clinically important because interventions that lower right ventricular afterload or increase right ventricular contractility will be more therapeutically appropriate. Patients requiring left ventricular assist devices becasue of the post-cardiotomy syndrome commonly have biventricular dysfunction and would therefore benefit from biventricular mechanical support.[9]

Assessment of right ventricular function is important in congenital heart disease. Right ventricular dysfunction can be an important predictor of long term outcome as Fuster *et al* showed in a large surgical series of patients with tetralogy of Fallot.[11] More recently Redington *et al* studied patients before and after such repair and showed that pressure-volume loops are a useful indicator of right ventricular dysfunction and pulmonary regurgitation postoperatively. They also analysed right ventricular function by this technique in transposition of the great arteries after an atrial re-routing operation and after anatomical correction by the arterial switch.[13] This comparative study gave only preliminary observations and conclusions; longer term comparisons of studies of right ventricular function are needed.

The future

At present right ventricular volume and function can both be accurately assessed and more sophisticated and detailed analysis of such function can be obtained from the construction of pressure-volume loops. The use of such techniques in the future should be able to resolve many of the obvious and complex clinical questions about right ventricular dysfunction.

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Left ventricular filling characteristics in pulmonary hypertension: a new mode of ventricular interaction

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Abstract

***Objective*—To examine the effects of pulmonary hypertension on left ventricular diastolic function and to relate the findings to possible mechanisms of interdependence between the right and left sides of the heart in ventricular disease.**

***Design*—A retrospective and prospective analysis of echocardiographic and Doppler studies.**

***Setting*—A tertiary referral centre for both cardiac and pulmonary disease.**

***Patients*—29 patients with pulmonary hypertension (12 primary pulmonary hypertension, 10 pulmonary fibrosis, five atrial septal defect (ASD), and two scleroderma) were compared with a control group of 10 patients with an enlarged right ventricle but normal pulmonary artery pressure (six ASD, one after ASD closure, one ASD and pulmonary valvotomy, one tricuspid valve endocarditis and repair, and one pulmonary fibrosis). None had clinical or echocardiographic evidence of intrinsic left ventricular disease.**

***Main Outcome measures*—M mode echocardiographic measurements were made of septal thickness, and left and right ventricular internal cavity dimensions. Doppler derived right ventricular to right atrial pressure drop, and time intervals were measured, as were isovolumic relaxation time, and Doppler left ventricular filling characteristics.**

***Results*—The peak right ventricular to right atrial pressure gradient was (mean (SD)) 60 (16) mm Hg in pulmonary hypertensive patients, and 18 (5) mm Hg in controls. The time intervals P_2 to the end of the tricuspid regurgitation, and P_2 to the start of tricuspid flow were both prolonged in patients with pulmonary hypertension compared with controls (115 (60) and 120 (40) *v* 40 (15) and 45 (10) ms, p values $<0·001$). Pulmonary hypertensive patients commonly had a dominant A wave on the transmitral Doppler (23/29); however, all the controls had a dominant E wave. Isovolumic relaxation time of the left ventricle was prolonged in pulmonary hypertensive patients compared with controls, measured as both A_2 to mitral valve opening (80 (25) *v* 50 (15) ms) and as A_2 to the start of mitral flow (105 (30) *v* 60 (15) ms, p values $<0·001$). The delay from mitral valve opening to the start of transmitral flow was longer in patients with pulmonary hypertension (30 (15) ms) compared with controls (10 (10) ms, $p < 0·001$). At the time of mitral opening there was a right ventricular to right atrial gradient of 12 (10) mm Hg in pulmonary hypertensive patients, but this was negligible in controls (0·4 (0·3) mm Hg, $p < 0·001$).**

***Conclusions*—Prolonged decline of right ventricular tension, the direct result of severe pulmonary hypertension, may appear as prolonged tricuspid regurgitation. It persists until after mitral valve opening on the left side of the heart, where events during isovolumic relaxation are disorganised, and subsequent filling is impaired. These effects are likely to be mediated through the interventricular septum, and this right-left ventricular asynchrony may represent a hitherto unrecognised mode of ventricular interaction.**

The right and left ventricles cannot be considered independently of one another, and there is evidence of interaction in isolated perfused hearts,[1] whole animals,[2 3 4] and humans.[5 6] Experimental studies and animal models of acute and chronic right ventricular pressure overload have shown that the shape of both ventricles is altered as a result of leftward displacement of the interventricular septum. Also, some echocardiographic studies have shown that patients with right ventricular pressure or volume overload often have impaired left ventricular diastolic function that has been related to the geometrical distortion of the left ventricle.[7 8 9]

The aim of this study was to show the abnormalities of left ventricular diastolic function present in a group of patients with right ventricular pressure overload secondary to severe pulmonary hypertension, and to compare these with a control group of patients with right ventricular dilatation but normal pulmonary artery pressures. In this way we hoped to study the possibility of right ventricular disease affecting left ventricular diastolic function, and in particular to separate any direct effects of pulmonary hyper-

Table 1 Characteristics of the study groups

	Pulmonary hypertension (n = 29)	*Right ventricular dilatation (n = 10)*
Age (y) (mean (SD))	44 (13)	42 (18)
Aetiology	Primary pulmonary hypertension (12)	Atrial septal defect (8)
	Pulmonary fibrosis (10)	Tricuspid valve endocarditis and repair (1)
	Atrial septal defect (5)	Pulmonary fibrosis (1)
	Scleroderma (2)	

tension from those of right ventricular dilatation, septal shift, or left ventricular compression.

Patients and methods

STUDY POPULATION

We studied 29 patients (age (mean (range)) 44 (20–63); 17 women) with pulmonary hypertension (12 primary pulmonary hypertension, 10 pulmonary fibrosis, five atrial septal defect (ASD), and two scleroderma), and a control group of 10 patients (age (mean (range)) 42 (17–57); 6 women) with right ventricular dilatation (free wall to septal diameter >2·6 cm at end systole) but normal pulmonary artery pressure (peak right ventricular to right atrial pressure drop <35 mm Hg). Table 1 shows the composition of each group. All patients were in sinus rhythm and all had holosystolic tricuspid regurgitation detectable on Doppler. The two patients with scleroderma had no features to suggest involvement of the left ventricle, and there was no hypertrophy of the free wall. No clinical or echocardiographic signs of intrinsic left ventricular disease were found in any other patients. The patients were young and none had symptoms suggestive of coronary artery disease; in the absence of clear clinical indications coronary angiography was not performed.

M MODE AND CROSS SECTIONAL ECHOCARDIOGRAPHY

M mode and cross sectional echocardiograms were taken with the patient in the standard left lateral position, using an Advanced Technical Laboratory Imager Mk 300I with a 3·0 MHz mechanical transducer, or a Toshiba SSH 160A imager with a 3·5 MHz transducer. Phonocardiograms were recorded from a Leatham microphone with a low frequency filter. M mode echocardiograms were recorded with simultaneous electrocardiogram and phonocardiogram on a Honeywell (Ecoline 22) strip chart recorder at a paper speed of 10 cm/s. Aortic valve closure (A_2) was taken as the start of the first high frequency vibration of the aortic component of the second heart sound recorded on the phonocardiogram, and was checked for validity with the aortic echogram and the aortic closure artefact on the Doppler recordings. Left ventricular internal cavity dimensions, septal and posterior wall thickness were measured with leading edge methodology, from the parasternal long axis view at end systole (at A_2) and end diastole (start of the QRS complex on the electrocardiogram). The right ventricle was measured from end diastolic frames of the apical four chamber view. The short axis was measured transversely at the tip of the tricuspid valve leaflets. Isovolumic relaxation time for the left ventricle was measured from A_2 to the initial separation of the mitral cusps on the M mode echogram. Interventricular septal motion was analysed from M mode echocardiograms taken at the level of the tips of the mitral leaflets. All measurements were made on three cardiac cycles and the mean was taken.

DOPPLER ECHOCARDIOGRAPHY

We recorded Doppler signals on a Doptek Spectrascan with a 2·0 MHz transducer, and a Toshiba SSH 160A with a 3·5 MHz transducer. Peak transmitral and transtricuspid flow velocities were identified by continuous wave from the apex and were recorded in pulsed mode with a 3 mm gate and 250 Hz wall filter. The peak velocities of early "E wave" and atrial "A wave" transmitral flow were recorded and the ratio E/A was derived. Tricuspid regurgitant flow was identified and recorded in continuous mode from the apex. The peak instantaneous systolic pressure drop from right ventricle to right atrium was calculated with the modified Bernoulli equation from the peak velocity of the tricuspid regurgitant signal, and the pressure drop at the instant of mitral cusp separation was also recorded. The RR interval was measured from the electrocardiogram, recorded simultaneously with the phonocardiogram. A second measurement of isovolumic relaxation time was obtained for the left ventricle from A_2 to the start of mitral flow. The first high frequency vibration of the second component of the second heart sound was taken as P_2 and this was checked on the pulmonary echogram and pulmonary closure artefact on Doppler recordings. The time interval from pulmonary closure (P_2) to the start of tricuspid flow was recorded in all cases. All measurements were made on three cardiac cycles and the mean taken. Intracavity flow was detected within the left ventricle with pulsed Doppler aligned along the ventricular inflow. Having identified flow in pulsed mode, it was recorded in colour Doppler superimposed upon a long axis M mode of the left ventricular cavity from the mitral ring to the apex.

STATISTICAL ANALYSIS

All values are given as mean (SD). Differences between mean values were compared by Student's *t* test, and those in incidence by Fisher's exact probability test.

Results

Tables 2 and 3 show mean values of the measurements. No significant differences were found between the ages or heart rates of pulmonary hypertensive patients and controls.

M MODE AND DOPPLER MEASUREMENTS

Dimensions and septal motion

The internal cavity dimensions of the left ventricle were equally reduced (by the enlarged right ventricle) in both groups of patients, although the septal thickness was greater in

Table 2 M mode measurements of dimensions of the left and right ventricles (mean (SD))

Variable	*Pulmonary hypertension (n = 29)*	*Right ventricular dilatation (n = 10)*	*p Value*
Left ventricular end diastolic dimension (cm)	3·5 (0·8)	3·8 (0·4)	NS
Left ventricular end systolic dimension (cm)	2·3 (0·5)	2·3 (0·4)	NS
Septal thickness at Q wave (cm)	1·2 (0·2)	0·9 (0·1)	0·001
Posterior wall thickness (cm)	1·0 (0·5)	0·8 (0·1)	NS
Right ventricular dimension (short axis) (cm)	2·6 (0·5)	2·9 (0·6)	NS
Posterior septal displacement after A_2 (n)	20	0	0·001

patients with pulmonary hypertension than in controls (1·24 (0·2) *v* 0·9 (0·1) cm, p < 0·001). In 20 of 29 (69%) patients with pulmonary hypertension, early diastolic posterior displacement of the septum was evident on M mode recordings, during isovolumic relaxation of the left ventricle (fig 1). This was not seen, however, in any patients of the control group (20/29 *v* 0/10, p < 0·0001). There were no significant differences in the peak systolic right ventricular to right atrial gradient or left ventricular filling pattern between those patients with and without diastolic posterior displacement of the septum.

Dynamics of tricuspid regurgitation and time intervals

By definition, the peak right ventricular to right atrial pressure gradient was higher in pulmonary hypertensive patients than in controls (60 (16) *v* 18 (5) mm Hg). Tricuspid regurgitation was prolonged in pulmonary hypertensive patients, persisting a mean of 75 ms after opening of the mitral valve, compared with only 20 ms in controls. Not only did this reduce the time available for forward tricuspid flow (240 (100) ms in pulmonary hypertensive patients *v* 360 (110) ms in controls, p = 0·012) but, when correlated with events on the left side of the heart, led to a tricuspid pressure drop (ventricular to atrial) of 12 (10) mm Hg still persisting at the time of opening of the mitral valve (compared with 0·4 (0·3) mm Hg in controls, p < 0·001) (figs 1 and 2). This occurred in spite of isovolumic relaxation time of the left ventricle being longer in pulmonary hypertensive patients than controls, whether measured from A_2 to opening of the mitral valve (80 (25) *v* 50 (15) ms) or from A_2 to the start of mitral flow on Doppler (105 (30) *v* 60 (15) ms, p < 0·001). Similarly, the time from pulmonary closure to the start of tricuspid flow on Doppler was prolonged in pulmonary hypertensive patients compared with controls (120 (40) *v* 45 (10) ms, p < 0·001). Further significant delay occurred in the start of mitral flow with respect to mitral cusp separation in pulmonary hypertensive patients compared with controls (30 (15) *v* 10 (10) ms, p < 0·001).

Filling patterns

On the transmitral Doppler 23/29 (79%) of the patients with pulmonary hypertension had a dominant "A" wave (23/29 "A fillers"). This pattern of filling was not found in any of the control group, who were all "E fillers"; the difference in incidence was highly significant (p < 0·0001). We found no significant difference in heart rate between the two groups of patients. Within the group with pulmonary hypertension, "A fillers" had a longer isovolumic relaxation time than the "E fillers" (100 (25) *v* 60 (20) ms, p < 0·001).

Intracavity flow

In six patients with pulmonary hypertension, intracavity flow was noted during isovolumic relaxation. All six patients showed posterior displacement of the interventricular septum after aortic closure. Compared with the group as a whole, no significant differences occurred in duration of isovolumic relaxation, ventricular filling times, or filling pattern in patients with intracavity flow.

Discussion

In common with previous studies, we have found impaired left ventricular diastolic function in our patients with pulmonary hyperten-

Table 3 Doppler and M mode characteristics (mean (SD))

Variable	*Pulmonary hypertension (n = 29)*	*Right ventricular dilatation (n = 10)*	*p Value*
RR Interval (ms)	660 (250)	750 (130)	NS
RV-RA pressure drop (mm Hg)	60 (16)	18 (5)	<0·001
Left ventricular isovolumic relaxation time (ms):			
A2-MVO	80 (25)	50 (15)	<0·001
A2-MV flow	105 (30)	60 (15)	<0·001
P2-TV flow (ms)	120 (40)	45 (10)	<0·001
A2-end of TR (ms)	155 (60)	70 (15)	<0·001
P2-end of TR (ms)	115 (60)	40 (15)	<0·001
RV-RA pressure drop at MVO (mm Hg)	12 (10)	0·4 (0·3)	<0·001
Mitral filling velocity:			
E (m/s)	0·3 (0·2)	0·6 (0·3)	<0·002
A (m/s)	0·55 (0·2)	0·4 (0·1)	<0·002
E/A ratio	0·5 (0·4)	1·8 (0·9)	<0·001
Delay in onset of mitral flow (MVO-MV flow) (ms)	30 (15)	10 (10)	<0·001

RV, right ventricle; RA, right atrium; MVO, mitral valve opening; MV, mitral valve; TV, tricuspid valve; TR, tricuspid regurgitation.

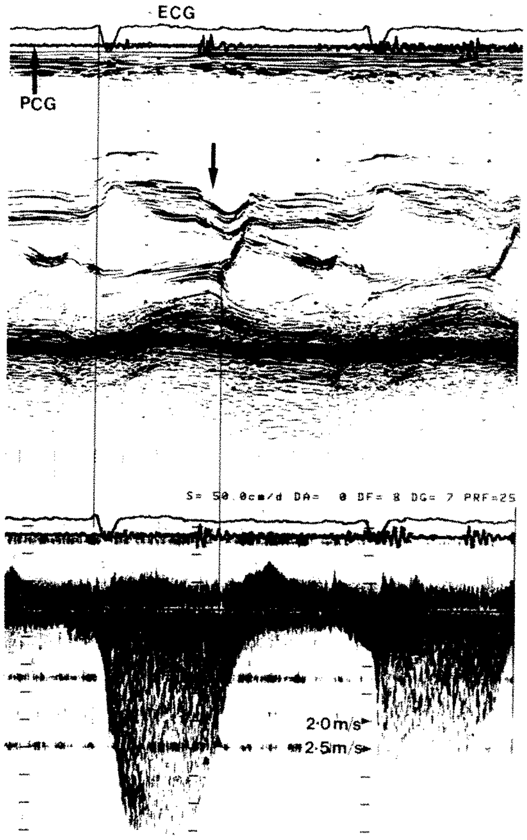

Figure 1 M mode echocardiogram of the left ventricular cavity (above), and continuous wave Doppler display of tricuspid regurgitation (below), from a patient with pulmonary hypertension. Note the posterior displacement of the interventricular septum (arrowed). This septal "dip" occurs during isovolumic relaxation of the left ventricle. Note that at the instant of mitral valve opening, tricuspid regurgitation continues, with a velocity of 2·25 m/s, corresponding to a right ventricular to right atrial pressure difference of 20 mm Hg. Electrocardiogram (ECG) and phonocardiogram (PCG) are shown.

sion.[8 9 10] As well as confirming well recognised disturbances of ventricular filling with reduced early diastolic and increased atrial velocities, we also found that isovolumic relaxation was abnormal. The interval from aortic closure to mitral cusp separation was significantly increased, and a further abnormal delay occurred between cusp separation and the earliest start of detectable transmitral flow by pulsed Doppler. Also, ventricular dimension characteristically fell during isovolumic relaxation, indicating a change in cavity shape, and in six patients, intracavity flow was detected.

Several mechanisms have been proposed to explain how right sided abnormalities can disturb left ventricular diastolic function in the absence of left ventricular diastolic disease. Distension or hypertrophy of the right ventricle may compress the left, thus altering chamber stiffness. Raised diastolic pressures from the right may directly affect those of the left, possibly by moving the septum, or the interaction may be indirect and involve the pericardium. In our study we aimed to investigate these possibilities in more detail.

The characteristic disturbances of isovolumic relaxation that we saw in our patients suggest that whatever the mode of interaction between the two ventricles it was already operating before mitral valve opening. This makes it unlikely that the primary disturbance was simply one of passive ventricular pressure and volume relations. Neither did pericardial restraint appear to be important as this is also a late diastolic phenomenon and it is difficult to see how such restraint could possibly affect isovolumic relaxation. Our patients all showed the characteristic anatomical findings of right ventricular dilatation with corresponding compression of the left ventricle, often with reversed septal motion. To investigate this possible mechanism we used a control group of patients with identical anatomical abnormalities, but in whom right ventricular systolic pressures were normal. Left ventricular diastolic function was effectively normal in this group. We concluded, therefore, that disturbed left ventricular diastolic function in our patients with pulmonary hypertension could not be attributed to reduced right ventricular diastolic compliance, pericardial interaction, left ventricular compression, or any other direct result of right ventricular dilatation, but seemed to be much more closely related to the presence of the pulmonary hypertension itself.

Not only is peak pressure in the pulmonary artery raised in patients with pulmonary hypertension, but the rate of fall is reduced,[11] so the pressure pulse lasts longer. This may show itself in several ways. The interval from pulmonary valve closure to tricuspid opening is increased[12 13] and the duration of the Doppler signal of functional tricuspid regurgitation is strikingly prolonged so that it may persist 100 ms or more after P_2. These findings are so consistent that they can be used to estimate peak pressure in the right ventricle in individual patients.[13-15] Effectively, therefore, pulmonary hypertension causes decline of right ventricular tension to be prolonged; with tricuspid regurgitation as a marker, this prolongation beyond pulmonary closure is considerable, being on average 3 ms for every 1 mm Hg rise in pressure in the right ventricle.[15] In our present study we were particularly concerned to examine the effects on left sided events. We found that tricuspid regurgitation consistently continued beyond open-

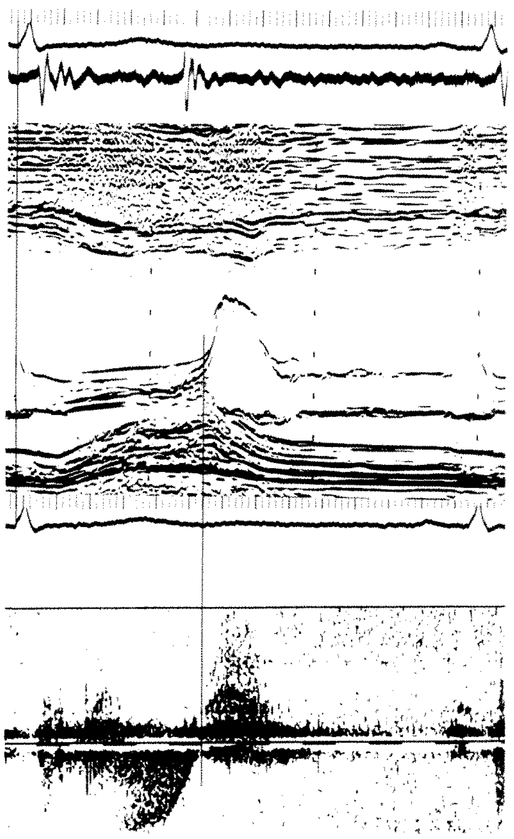

Figure 2 M mode echocardiogram of the left ventricular cavity (above), and continuous wave Doppler display of tricuspid regurgitation (below), from a control patient with dilatation of the right ventricle and normal pulmonary artery pressure. Note that at the instant of opening of the mitral valve, tricuspid regurgitation has ceased, by contrast with the prolonged tricuspid regurgitation shown in fig 1.

ing of the mitral valve, and that at the time of mitral cusp separation a mean gradient of 12 mm Hg from right ventricle to right atrium still existed. Thus tension in the right ventricle continues to decline throughout, and beyond isovolumic relaxation of the left ventricle. It is likely that tension within the interventricular septum is equally prolonged. This would explain the displacement of the posterior septum and associated fall in the dimension of the left ventricle seen in the patients with pulmonary hypertension but not in the controls. This septal shift will have contributed to the incoordinate wall motion seen during isovolumic relaxation, and thus to delaying the opening of the mitral valve and the start of filling as well as to the abnormal intracavity flow.

The period of isovolumic relaxation is critical to normal filling. Prolonged or disorganised isovolumic relaxation has important consequences on function later in diastole, reducing early velocity diastolic filling and causing a corresponding increase in velocity during atrial systole. This effect has been shown in hypertrophic cardiomyopathy,[16] coronary artery disease,[17] and left ventricular hypertrophy due to aortic stenosis.[18] We suggest that our findings represent yet another example of the interaction between isovolumic relaxation and ventricular filling, and as the disturbances in filling of the left ventricle were so typical of those previously described, we think that no other explanation for them need be sought. Even within our group of patients with pulmonary hypertension, "A fillers" had a significantly longer isovolumic relaxation time than "E fillers". The effects of a diastolic pressure gradient across the septum on ventricular septal motion have been recognised for some time, both in whole animals,[2] and humans with pulmonary hypertension,[6] but such gradients have been associated with raised right ventricular diastolic pressure due to disturbed compliance and thus occur during ventricular filling; hence they are different in their mechanism and timing to those we have described. Similarly, left ventricular asynchrony has been recognised in pulmonary hypertension,[10] but again this was only apparent during filling and events during isovolumic periods were specifically excluded from this study. That a pressure gradient across the septum may disorganise isovolumic relaxation and thus disturb filling does not appear to have been previously proposed.

This study highlights a potential problem of nomenclature that will become increasingly important once it is recognised that systole and diastole need not be synchronous on the two sides of the heart. In our patients decline of right ventricular tension during late systole corresponded to early left ventricular diastole and this asynchrony had important practical consequences. It, in fact, represents a novel mode of ventricular interaction that has received little attention, and it also provides further evidence of the importance of isovolumic relaxation of the left ventricle in determining events for the remainder of diastole.

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Vasodilator myocardial perfusion imaging: demonstration of local electrophysiological changes of ischaemia

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Abstract

***Objective*—To examine the incidence and severity of myocardial ischaemia provoked in the course of perfusion scintigraphy by coronary vasodilators using endocardial recordings of steady state monophasic action potentials as an independent marker of early localised myocardial ischaemia.**

***Patients*—31 men undergoing routine cardiac catheterisation for investigation of chest pain were studied.**

***Setting*—A tertiary cardiac referral centre.**

***Design*—Single site monophasic action potentials were recorded from the left or right ventricle or both (50 recording sites) during intravenous infusion of dipyridamole (0·015 mg/kg/min) for four minutes. Heart rate was held constant with atrial pacing at 20% above the patient's resting rate. Technetium-99m hexakis-2-methoxy-2-methylpropyl-isonitrile (MIBI) was administered four minutes after dipyridamole, and single photon emission tomographic imaging was performed an hour later. Rest images were obtained the next day (two day, two dose protocol). Recordings were divided into three groups based on the scintigraphic perfusion characteristics and coronary anatomical data for the action potential recording site: group 1—recordings from areas with a normal perfusion pattern (n = 30), group 2—recordings from areas with a perfusion defect and subtended by significantly narrowed coronary arteries without obvious angiographic collateral supply (n = 10), and group 3—recordings from areas with a perfusion defect and subtended by occluded arteries with angiographically evident collaterals from adjacent vessels (n = 10).**

***Results*—There were changes in the duration of the monophasic action potential indicative of ischaemia—that is, shortening of duration of steady state action potential—in 18 of the 20 recordings from areas of abnormal perfusion. Peak changes were apparent eight minutes from the start of the dipyridamole infusion. Mean (SEM) values for duration of the action potential between control and peak effect at eight minutes were 276·5 (5·3) ms *v* 276·6 (5·4) for group 1 (NS), 289·6 (4·7) ms *v* 278·4 (4·9) ms for group 2 ($p < 0·001$), and 269·6 (5·7) ms *v* 242·0 (4·4) for group 3 ($p < 0·0001$). These changes were significantly different between the three groups ($p < 0·01$). ST segment changes on the surface electrocardiogram were seen in only eight patients, all with areas of viable myocardium supplied by collateral vessels.**

***Conclusions*—These data provide strong evidence for the presence of myocardial ischaemia in regions of reversible perfusion defects induced by dipyridamole. This study also shows that such ischaemia is more intense and more likely to be seen when myocardial viability is dependent on collateral circulation.**

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Myocardial perfusion scintigraphy using vasodilators such as dipyridamole or adenosine is a widespread diagnostic tool although the underlying pathophysiological mechanisms remain incompletely defined.[1–3] Both dipyridamole and adenosine dilate coronary arteries and produce a substantial increase in coronary blood flow.[4 5] In coronary vascular beds distal to a flow limiting stenosis, autoregulatory mechanisms operate producing maximal vasodilatation under resting conditions and thereby limiting coronary flow reserve.[6] Dipyridamole, for example, would therefore induce a preferential dilatation in the vascular bed subtended by normal arteries but exert minimal effects on those distal to a stenotic artery.[5] These regional differences in blood flow would unevenly distribute added radiotracers, producing scintigraphic images within which areas of low tracer uptake are conventionally interpreted as being ischaemic. Pharmacological vasodilatation, unlike exercise perfusion scintigraphy, produces an increase in coronary supply exceeding demand and areas of relative hypoperfusion may not necessarily be ischaemic. Furthermore, in clinical use, dipyridamole is seldom associated with obvious symptoms of myocardial ischaemia.[7 8] Such findings have led to the suggestion that dipyridamole causes little, if any, myocardial ischaemia.

Development of transient asynergic wall motion in regions of the left ventricle is relatively specific in myocardial ischaemia.[9]

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This occurs in 50% to 60% of patients with significant coronary artery disease when given dipyridamole, and is evidence that myocardial ischaemia is at least partly a function of pharmacological coronary vasodilatation.[10 11] Physiological mechanisms for the occurrence of ischaemia have been put forward,[12-14] but the true incidence of ischaemia with dipyridamole remains undefined. The definition of ischaemia within vasodilator perfusion imaging is important as the technique is gaining popularity and dipyridamole has been licensed for this purpose. Because dipyridamole produces perfusion deficits in regions of mild to moderate coronary stenosis pathophysiological importance of such lesions needs to be examined.[15] We have used endocardial recordings of monophasic action potentials as an electrophysiological marker of localised ischaemia, to document the presence or absence of ischaemia in areas of perfusion deficits induced by dipyridamole. The duration of the monophasic action potentials measured under steady state conditions registers early changes of localised myocardial ischaemia, by shortening in response to ischaemia.[16 17] Recordings were made from the left, or right ventricular endocardium, or both during the administration of dipyridamole, and electrophysiological changes indicative of ischaemia were recorded in areas of myocardium with reversible perfusion defects as shown by technetium-99m hexakis-2-methoxy-2-methypropyl-isonitrile (Tc-99m MIBI) and tomography.

Patients and methods

After routine cardiac catheterisation, monophasic action potentials from the ventricular endocardium were recorded during intravenous infusion of dipyridamole. When the drug was expected to exert maximal pharmacological effect (four minutes after dipyridamole infusion), Tc-99m MIBI was given for single photon emission computed tomographic imaging. The position of the catheter recording monophasic action potentials in the ventricle was found by biplane cinematography. Changes in the duration of the action potential were then related to the perfusion characteristics in the area of the recording.

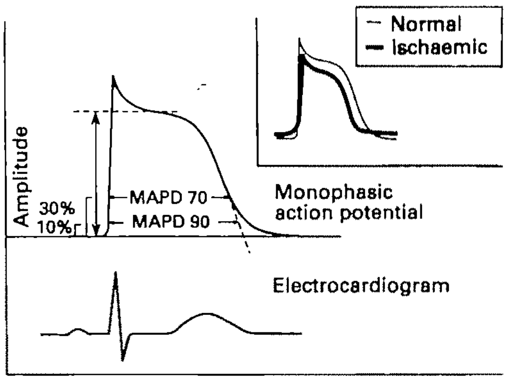

Figure 1 Typical monophasic action potential signal. The electrocardiogram is shown below the signal to indicate the temporal relation to the QRST. The amplitude of the signal (mV) is the distance between the diastolic baseline and the highest point on the plateau of the repolarisation phase. The duration of the action potential at 70% (MAPD 70) and 90% (MADP 90) repolarisation is measured with reference to the amplitude. The inset in figure 1 shows classic configurational changes in the action potential signal with ischaemia.

STUDY PATIENTS

Thirty three patients undergoing routine cardiac catheterisation for investigation of chest pain were selected at random from the waiting list. Patients with unstable angina, atrial fibrillation, overt congestive heart failure, and obstructive airways disease were excluded from the study. Antianginal drugs were continued up to 12 hours before the study. Substances containing methyl xanthines were withheld for 24 hours before the study. Written informed consent was obtained from each patient and the study protocol was approved by our institution's ethical committee.

ELECTROPHYSIOLOGICAL MEASUREMENTS

Purpose built bioplar pressure contact catheters with silver and silver chloride electrodes (Cordis (UK) Ltd; 7 French size) were used to record monophasic action potentials. Apposition of the exploring electrode to the endocardial surface resulted in stable action potential signals with an amplitude of 20 to 40 mV. Details of signal collection and processing have been previously described.[18]

Figure 1 shows a typical monophasic action potential signal and its time relation to the QRST of the electrocardiogram. The upstroke of the action potential is equivalent to the R wave and the downstroke (fast repolarisation phase) to the T wave of the electrocardiogram. The amplitude of the signal is measured in mV as the distance between the diastolic baseline and the highest part of the plateau phase of repolarisation. Duration is measured in ms with reference to the total amplitude of the signal. Any alteration in amplitude of the signal therefore has little influence on the duration measurement as both values would change proportionately. The inset in fig 1 depicts configurational changes in the signal with ischaemia. Although ischaemia also produces a fall in total amplitude and upstroke velocity of the action potential, shortening of the duration is the most reliable index as the monophasic action potential reflects only a variable proportion of the amplitude and upstroke velocity of the intracellular action potential.[19]

MYOCARDIAL SCINTIGRAPHY

Tc-99m MIBI was used for myocardial perfusion scintigraphy with single photon emission tomography using a two day, two dose protocol. Images were acquired with a single detector rotating gamma camera and computer system (IGE 400 AC-Starcam) equipped with a low energy, high resolution collimator. To get the images the following variables were used: a 20% energy window had a 3% offset around a 140 keV technetium-99m photopeak; 64 half minute views were acquired over a 360° circular arc of rotation starting at 45° right anterior oblique; data acquisition and storage was on a 128 × 128 word matrix; acquired data was prefiltered with a Hanning filter (0·75 cycles/cm) and transformed to a 64 × 64 word matrix. A back projection reconstruction algorithm was used to get transaxial sections (one pixel thick). These reconstructed tomographic slices were then reoriented in the short axis, horizontal long, and vertical long axes for display and visual analysis.

PROCEDURE

Routine left ventricular and coronary angiography was performed through the femoral route by the Judkin's technique with a non-ionic angiographic dye (Omnipaque 350, Nycomed (UK) Ltd). This was followed by positioning of catheters, for the measurement of monophasic action potentials, in the left, or right ventricular endocardium, or both, through the femoral arterial or venous sheaths. A bipolar temporary pacing electrode was introduced into the right atrium through a second femoral venous sheath. Atrial pacing was established at 20% above the patient's resting heart rate to maintain a constant heart rate during the procedure.

Arterial blood pressure was monitored through the side arm of the femoral arterial cannula. The electrocardiogram with limb leads I and II and chest lead V5 was continuously monitored. Monophasic action potentials were recorded from a single site in the left, or right ventricle, or both after pacing had been established for three minutes (to allow for adaptation of the duration of the action potentials). Dipyridamole was infused through a forearm vein at a rate of 0·142 mg/kg/min over four minutes. Recordings of action potentials, arterial pressure, and electrocardiogram were made every minute for a total of 15 minutes.

Four minutes after completion of dipyridamole infusion, 370 MBq of Tc-99m MIBI was given intravenously. If any patient developed severe angina or haemodynamic upset, the effect of dipyridamole was reversed using 125 to 250 mg of aminophylline given intravenously two minutes after Tc-99m MIBI. Patients were returned to the ward and encouraged to eat a light fatty meal to facilitate clearance of the isotope from the liver. Myocardial perfusion imaging with tomography was carried out between one and two hours after injection of the tracer. Rest imaging was performed 24 hours later after the patient had fasted for four hours and after a second dose of 370 MBq of Tc-99m MIBI. Data collection was started one to two hours after injection following a light fatty meal.

DATA ANALYSIS

Coronary angiographic data were interpreted by visual inspection and the degree of stenosis was classed as mild, moderate, or severe. Regional collateral circulation was confirmed on the basis of retrograde filling of distal segments of totally or subtotally occluded arteries. Regions supplied by arteries with more than 50% stenosis (but non-occluded) and without angiographically obvious collateral circulation were designated areas without collateral vessels.

Myocardial perfusion images were analysed and interpreted by one observer blinded to the angiographic and monophasic action potential data. In case of equivocal results, a consensus opinion was accepted. Images were considered normal if they were without defect in the initial set or abnormal if there were reversible or fixed defects. Position of the defect was related to standard coronary anatomy where anterior and septal abnormalities were considered to be in the territory of the left anterior descending artery, lateral or posterolateral defects in the territory of the left circumflex artery, and inferior abnormalities in the territory of the right coronary artery. Apical defects could relate to the territory of any major coronary artery.[20]

The duration of the monophasic action potentials was measured by an observer blinded to the angiographic and scintigraphic data. Measurements were made at both 70% and 90% repolarisation. As both values registered a similar pattern, only values at 90% repolarisation are included in the text.

The position of the catheter measuring action potentials in the ventricle was documented by biplane cinematography at the time of cardiac catheterisation and was subsequently related to the perfusion abnormalities on the perfusion scan. Recordings were divided into three groups based on the relation of the catheter tip to areas of scintigraphic perfusion defects and coronary anatomical data for the action potential recording site; group 1 includes recordings from areas with a normal perfusion pattern; group 2 includes recordings from areas with reversible perfusion pattern but subtended by stenosed arteries without angiographically apparent collateral vessels; group 3 includes recordings from areas with reversible pattern but subtended by totally or subtotally occluded arteries with collateral filling of the distal vessel.

Statistical analysis of comparisons between groups were made by analysis of variance with planned comparison of the means (ANOVA). For graphical representation and to facilitate visual display, changes in duration of action potential were expressed as ratios: for each single site recording, the control value of duration of action potential was taken to represent 100% and any alteration was related to the control value. Pooled data are expressed as means (SEM).

Results

Of 33 patients studied, heart rate control during infusion of dipyridamole was lost in two patients and as the duration of action potential is dependent on cycle length, these two patients were excluded from the analysis. The results reported are on the 31 patients in whom steady state single site recordings of action potentials were obtained from the ventricles. The table gives patient details. Median age of the patients studied was 56 (range 33–72) years. All except two patients had significant coronary artery disease defined as greater than 50% stenosis in at least one major epicardial artery; 12 of these had single vessel disease, 12 two vessel disease, and five triple vessel disease. Previous aorto-coronary bypass grafting had been performed in three patients.

SENSITIVITY OF MYOCARDIAL PERFUSION SCINTIGRAPHY

All patients with significant coronary artery disease showed perfusion abnormalities on imaging. Among 51 coronary arteries with significant stenoses, 44 showed related per-

Details of patients (all men) in the study

Patient no	*Age*	*Drugs*	*Coronary artery anatomy*			*Paced rate (bpm)*	*Angina ST change*	*Perfusion scan*	*MAP catheter position*	*Group*
			LAD	*LCX*	*RCA*					
1	54	Atenolol Diltiaz	Moderate NC	Moderate NC	Severe NC	80	AP+ ST−	Inferior, lateral, and anteroapical RPD, septum normal	Lateral wall of LV RV mid-septum	LV-2 RV-1
2	44	Atenolol	Normal	Moderate NC	Occluded C	80	AP+ ST−	inferior FD lateral RPD	Lateral wall of LV RV mid-septum	LV-2 RV-1
3	58	Propran Nifed Nitrate	Moderate NC	Moderate NC	Occluded C	75	AP+ ST+	inferior RPD	RV mid-septum	RV-1
4	50	Atenolol Diltiaz	Severe NC	Normal	Occluded C	80	AP+ ST−	Inferior and anteroseptal RPD	Inferoposterior wall of LV	LV-3
5	56	Atenolol Nifed	Normal	Normal	Normal	80	AP+ ST−	Normal	RV mid-septum	RV-1
6	62	Atenolol	Normal	Moderate NC	Occluded C	80	AP− ST−	Inferior FD, lateral RPD	Posterolateral wall of LV; RV mid-septum	LV-2 RV-1
7	48	Atenolol	Moderate NC	Normal	Occluded C	80	AP+ ST−	Inferior and antero apical RPD	Lateral wall of LV	LV-1
8	35	Atenolol Nitrate	Severe NC	Mild	Normal	80	AP− ST−	Anterior and septal RPD	Lateral wall of LV RV mid-septum	LV-1 RV-2
9	68	Metop Nifed	Severe NC	Normal	Severe NC	80	AP− ST−	Anterior, septal, and inferior RPD	Lateral wall of LV	LV-1
10	59	Atenolol	Severe NC	Moderate NC	Mild	90	AP+ ST−	Anterior and septal RPD	Lateral wall of LV RV mid-septum	LV-1 RV-2
11	49	Nil	Normal	Severe NC	Normal	100	AP+ ST−	Inferolateral RPD	Lateral wall of LV RV mid-septum	LV-2 RV-1
12	55	Atenolol Nifed	Mild	Occluded NC	Non Dominant	80	AP+ ST−	Inferior wall partial RPD	Lateral wall of LV RV mid-septum	LV-1 RV-1
13	57	Nifed	Mild	Occluded C	Normal	90	AP+ ST+	Inferior and lateral RPD	Lateral wall of LV RV mid-septum	LV-3 RV-1
14	50	Atenolol	Severe NC	Mild	Occluded C	90	AP+ ST+	Anteroseptal and inferior RPD	RV inferoposterior septum	RV-3
15	54	Atenolol Nifed	Normal	Normal	Normal	90	AP+ ST−	Normal	Lateral wall of LV RV apex	LV-1 RV-1
16	56	Atenolol Nifedip	Severe NC	Normal	Occluded C	80	AP+ ST−	Anteroseptal RPD, inferior FD	Lateral wall of LV RV mid-septum	LV-1 RV-2
17	50	Nil	Mild	Moderate NC	Severe NC	100	AP+ ST−	Inferior and lateral RPD	Lateral wall of LV RV mid-septum	LV-2 RV-1
18	58	Metop	Poor graft run off-NC	Normal	Normal	80	AP− ST−	Anteroseptal partial RPD	RV apical septum	RV-2
19	68	Metop	Occluded C	Occluded C	Patent graft	90	AP+ ST+	Anterior FD, lateral wall RPD	Lateral wall of LV	LV-3
20	57	Metop Diltiaz	Moderate NC	Normal	Normal	90	AP+ ST−	Anteroapical RPD, septum normal	RV mid-septum	RV-1
21	33	Atenolol	Moderate NC	Normal	Normal	80	AP+ ST−	Mild anteroapical RPD	LV septum RV mid-septum	LV-1 RV-1
22	59	Atenolol Nifed	Occluded C	Normal	Normal	100	AP+ ST−	Anterior and septal RPD, inferior partial RPD	Lateral wall of LV RV mid-septum	LV-1 RV-3
23	54	Atenolol	Occluded C	Normal	Moderate NC	80	AP+ ST−	Anterior, septal, and inferior RPD	Lateral wall of LV RV anterior wall	LV-1 RV-1
24	54	Nil	Occluded C	Occluded C	Normal	90	AP+ ST+	Anteroapical FD, lateral wall RPD, septum normal	Lateral wall of LV RV mid-septum	LV-3 RV-1
25	46	Diltiaz	Normal	Occluded C	Non Dominant	80	AP+ ST+	Lateral wall RPD, partial RPD in inferoapical region	Lateral wall of LV RV posterior septum	LV-3 RV-3
26	60	Atenolol Diltiaz	Mild	Normal	Severe NC	100	AP+ ST−	Inferior and apical RPD	Lateral wall of LV RV apex	LV-1 RV-1
27	48		Moderate NC	Moderate NC	Occluded NC	110	AP− ST−	Anteroseptal FD, inferior RPD	Lateral wall of LV RV apex	LV-1 RV-1
28	72	Nifed	Occluded C	Moderate NC	Occluded C	90	AP+ ST+	Anterseptal RPD, inferior FD	RV mid-septum	RV-3
29	66	Atenolol Nifed	Patent graft	Patent graft	Occluded C	90	AP− ST−	Inferior wall partial RPD	RV mid-septum	RV-1
30	59	Atenolol Nifed	Normal	Normal	Severe NC	70	AP− ST−	Inferior wall and inferior septal RPD	RV posteroinferior septum	RV-2
31	64	Atenolol Nifed	Severe C	Moderate NC	Occluded C	70	AP+ ST+	Inferior wall FD, anteroseptal RPD	High lateral wall of LV; RV mid-septum	LV-1 RV-3

Diltiaz, diltiazem; Propran, propranolol; Nifed, nifedipine; Metop, metoprolol; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; NC, without collateral vessels; C, with collateral vessels; AP, angina pectoris; ST, ST segment of electrocardiogram; FD, fixed defect; RPD, reversible perfusion defect; MAP, monophasic action potential; LV, left ventricle; RV, right ventricle.

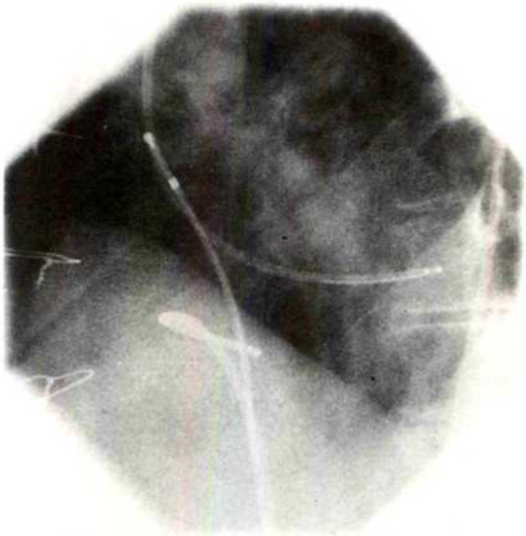

Figure 2 Typical catheter placements shown in the left anterior oblique view. Recording catheters were placed in the right and left ventricles. The right ventricular catheter has been manipulated on to the interventricular septum and in the left ventricle the catheter has been left in contact with the endocardium of the lateral wall. A temporary pacing catheter is shown in the right atrium.

fusion abnormalities on scintigraphy thus yielding a per vessel sensitivity of 86·3%. When fixed defects due to previous myocardial infarction were excluded, the sensitivity fell to 83·7%.

MONOPHASIC ACTION POTENTIAL RECORDINGS

Figure 2 shows typical catheter placements during recording of action potentials. Fifty single site recordings were obtained from 31 patients (simultaneous recordings from right and left ventricles in 19 patients, the left ventricle alone in four patients, and right ventricle alone in eight patients). Based on the perfusion characteristics of the recording site, 30 recordings were assessed to be from normally perfused areas (group 1). Of the 20 recordings from abnormally perfused areas, 10 were from areas without collateral vessels (group 2), and 10 from areas with collaterals (group 3). Although the pacing rates used in each set of recordings varied, there was no significant difference in the paced heart rates between the three groups (mean (SE) values: group 1 87·8 (1·9), group 2 84 (3·0), and group 3 86 (2·7); NS).

Shortening of the duration of the action potential occurred in eight of the 10 recordings in group 2 and all recordings in group 3. Maximal changes were apparent eight minutes from the start of dipyridamole infusion. Figure 3 shows an example of the development and regression of the duration of the action potential that has shortened indicating ischaemia. Patient 19 had occlusion of native vessels and grafts to the territory of the left coronary circulation. Vessels from the right coronary artery and graft had formed collaterals to the territory of the left coronary circulation. Dipyridamole infusion produced considerable angina and ischaemic changes in recordings of monophasic action potentials from the lateral wall of the left ventricle. Shortening of the duration of the action potential was maximal at eight minutes. Regression of changes was apparent at 12 minutes, in this case acclerated by 125 mg of aminophylline at 10 minutes.

ILLUSTRATIVE STUDIES

Figures 4 and 5 show coronary angiographic appearances, tomographic myocardial perfusion images, and typical examples of changes in monophasic action potential in studies representative of the three groups. Figures 4 A–D are data on patient 11 in table 1. Coronary angiography shows normal right coronary and left anterior descending arteries producing a normal perfusion pattern in areas subtended by these arteries. The left main circumflex artery has a tight lesion without collateral supply. Perfusion images show reversible perfusion abnormalities in the lateral wall of the left ventricle. Monophasic action potentials recorded from the normally perfused septum show no change in the duration of the signals whereas those from the abnormally perfused lateral wall of the ventricle show shortening of the duration by 16 ms. Figures 5 A–D are from patient 22. The left anterior descending artery is occluded at its origin. The region has collateral vessels fed by the right coronary artery. A large area of defective perfusion in the anterior and septal regions is produced with dipyridamole which partially reverses on the rest images. The duration of the action potentials recorded from the right ventricular septum show shortening by 40 ms whereas those from a normally perfused left ventricular lateral wall remain unchanged.

ANALYSIS OF POOLED DATA

The duration of the monophasic action potentials measured at 90% repolarisation altered from a control mean (SEM) of 276·5 (5·3) ms to 276·6 (5·4) ms for group 1 (NS), 289·6 (4·7) ms to 278·4 (4·9) for group 2 recordings ($p < 0{\cdot}001$) and 269·6 (5·7) ms to 242·0 (4·4) for group 3 recordings ($p < 0{\cdot}0001$). Figure 6 shows the changes in action potential compared with the control values during dipyridamole infusion in the three groups. Significant ischaemia is apparent in the group 2 recordings

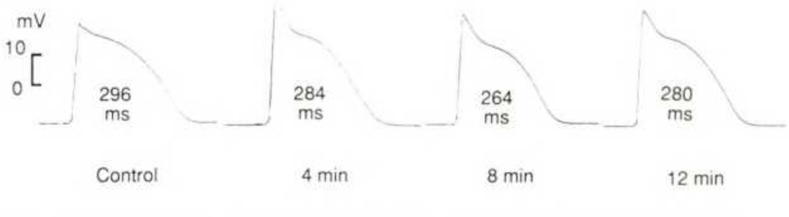

Figure 3 Serial steady state monophasic action potential signals recorded from the lateral left ventricular wall in patient 19 with occlusion of the native vessels and grafts to the territory of the left coronary circulation. This territory was perfused by collateral vessels from the right coronary artery and graft. Dipyridamole infusion produced noticeable shortening of the action potential duration, which becomes apparent four minutes from the start of dipyridamole infusion. Peak changes occur at eight minutes when the action potential duration shortens by 32 ms compared with the control value. Regression of these changes is seen at 12 minutes, in this case enhanced by the administration of 125 mg of aminophylline given at 10 minutes. Duration of monophasic action potentials in ms measured at 90% repolarisation (MADP 90) is shown within each action potential signal.

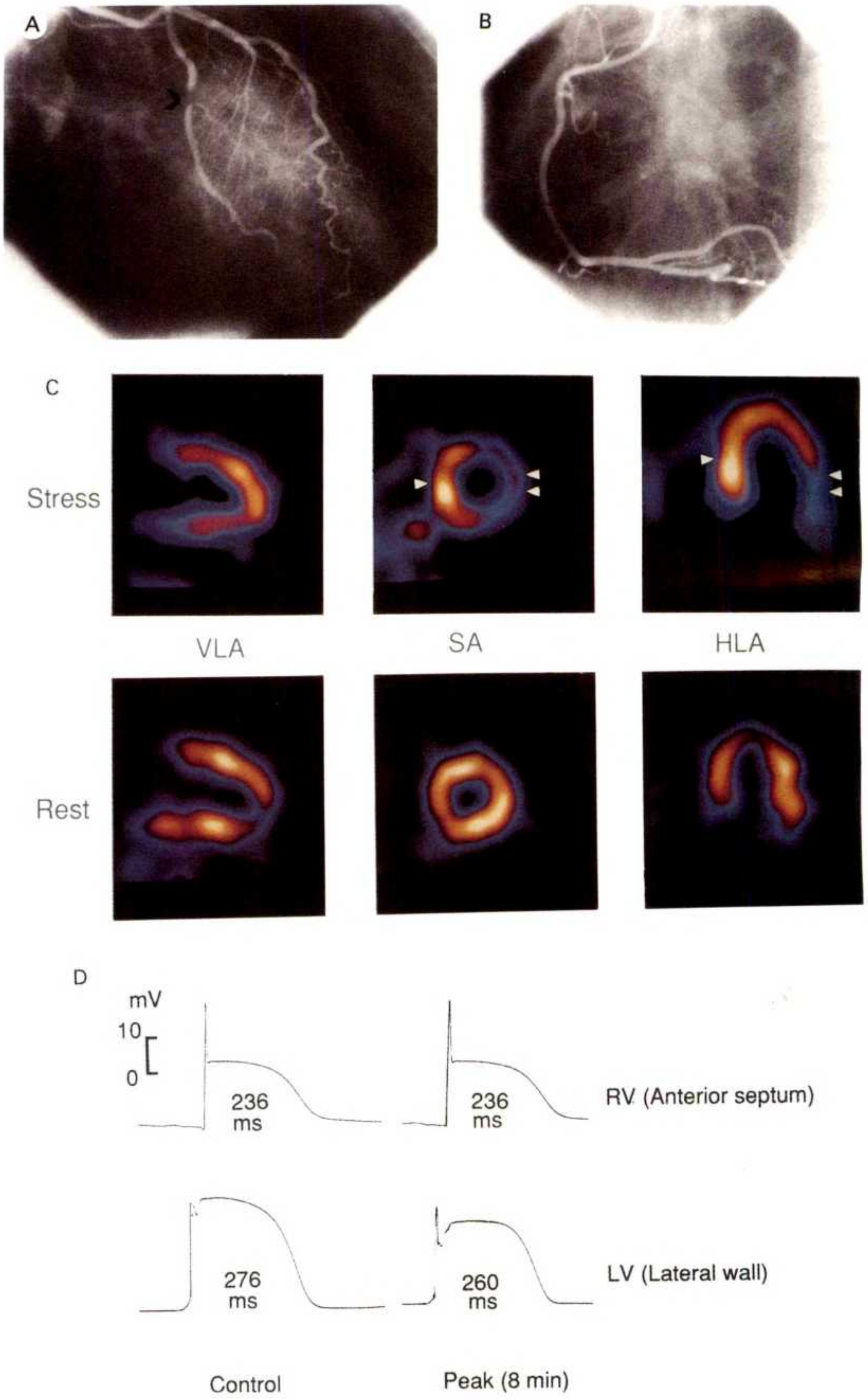

Figure 4 Coronary angiographic appearances, myocardial perfusion images (single photon emission tomography), and monophasic action potential signals at control and at peak effects of dipyridamole for patient 11. Figure 4A and B show a tight stenosis (arrow) in the proximal course of the left circumflex artery without obvious collateral supply to the area subtended by this artery. Figure 4C shows perfusion images with considerable lateral wall hypoperfusion during dipyridamole stress which reperfuses with rest. Figure 4D shows monophasic action potentials recorded simultaneously from the right ventricular mid-septum and left ventricular lateral wall (recording sites represented on the scintigram are indicated: single arrow for right ventricular septum and double arrows for left ventricular lateral wall). Duration of steady state action potential measured at 90% repolarisation (shown within signals) remains unchanged from the control value of the recording from the normally perfused septum whereas that for the area without collateral vessels but with abnormally perfused left ventricular lateral wall shortens by 16 ms. VLA, vertical long axis; SA, short axis; HLA, horizontal long axis.

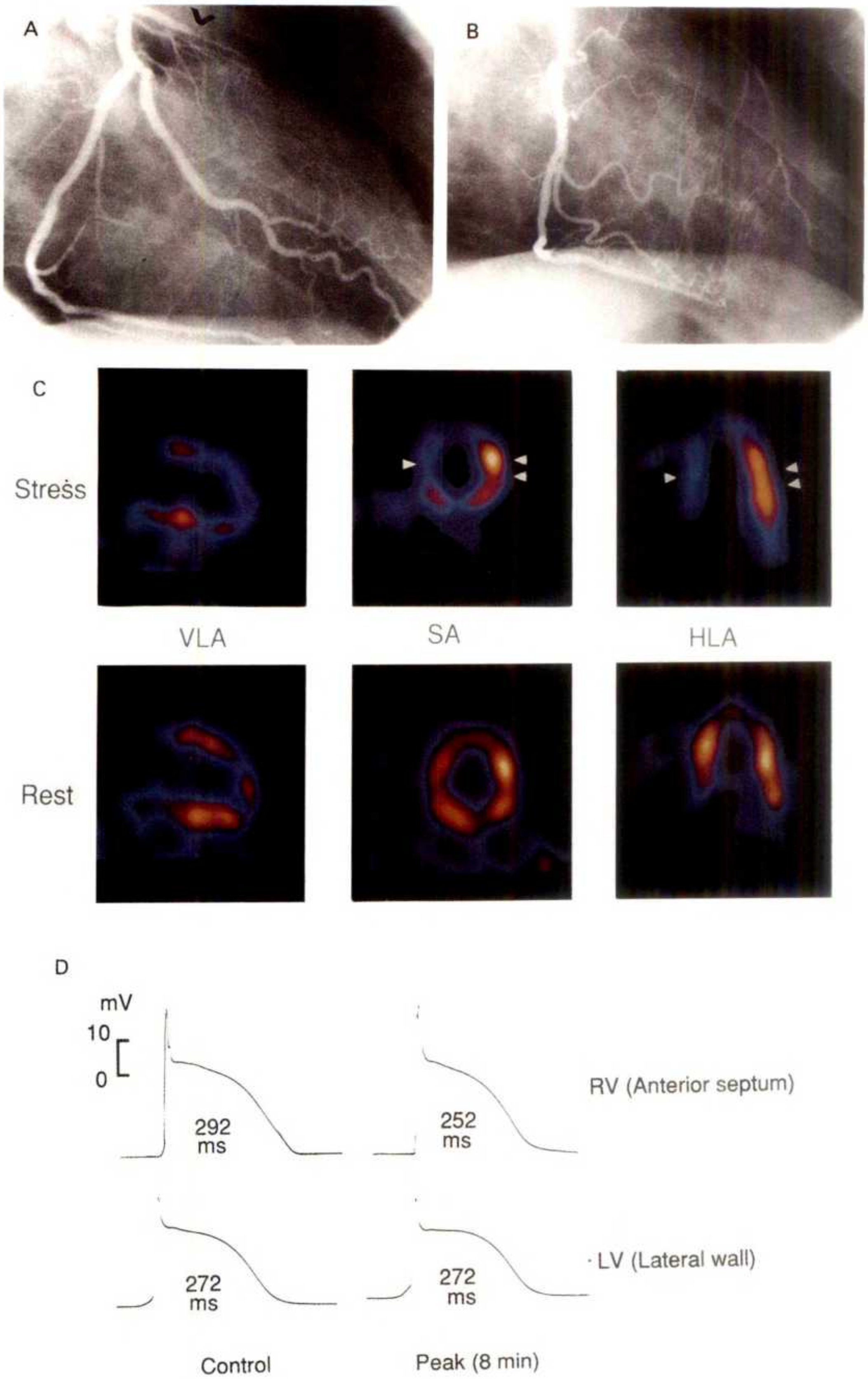

Figure 5 Coronary angiographic appearances, myocardial perfusion images (single photon emission tomography), and monophasic action potential signals at control and at peak dipyridamole effect for patient 22. Figure 5 shows occlusion of the left anterior descending artery at its origin ((A) arrow). The distal vessel is filled retrogradely by extensive collaterals from the normal right coronary artery (B). Perfusion images (figure 5C) show anterior, apical, and septal hypoperfusion during dipyridamole stress with partial reperfusion of these areas during rest. Figure 5D shows simultaneous action potentials recorded from the right ventricular septum and the left ventricular lateral wall (recording sites indicated by arrows on the scintigram: single arrow for right ventricular septum and double arrows for left ventricular lateral wall). Duration of steady state action potential of the right ventricle (abnormally perfused area with collateral vessels) measured at 90% repolarisation is 40 ms shorter than recordings from the normally perfused left ventricular lateral wall that show no alteration in the duration from control value (duration of action potentials shown within signals). VLA, vertical long axis; SA, short axis; HLA, horizontal long axis.

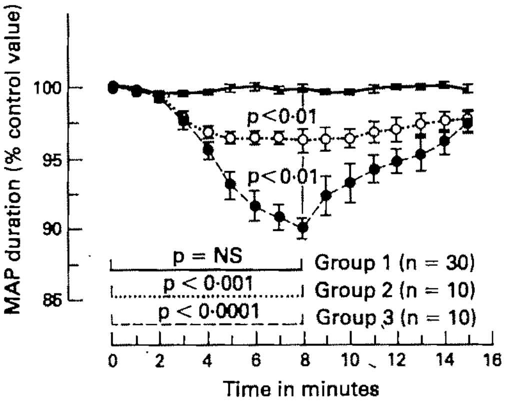

Figure 6 Mean changes in duration of the action potentials of the three groups are shown as a percentage of the control values. During infusion of dipyridamole, the group 1 (normal zone recordings) show no change. Group 2 (abnormal zone without collateral vessels) recordings shorten significantly when compared with group 1. The changes are maximal for group 3 (collateral blood flow in an abnormal zone) with significantly greater shortening of the action potentials than in groups 1 and 2. Peak changes are apparent eight minutes after the start of dipyridamole administration.

ischaemia is apparent in the group 2 recordings compared with group 1, but the extent of ischaemia is substantially greater for group 3 recordings (changes in duration of action potentials from control to the eight minute values were significantly different between the three groups $p < 0\cdot01$).

SIMULTANEOUS NORMAL AND ABNORMAL ZONE RECORDINGS

Simultaneous recordings were obtained from the right and left ventricles in 18 patients. In 12 of these, recordings were obtained from one normally and one abnormally perfused site. Mean (SEM) change in the duration of action potentials in ms between control values and eight minute values were as follows: 276·3 (10·2) *v* 276·0 (10·3) for group 1 ($n = 12$; NS); 287·5 (5·6) *v* 274·0 (4·9) for group 2 ($n = 8$; $p < 0\cdot0006$); 277·0 (8·7) *v* 244 (8·5) for group 3 ($n = 4$; $p < 0\cdot001$). These changes were significantly different between the three groups ($p < 0\cdot01$).

ANGINA AND ST SEGMENT CHANGES WITH INFUSION OF DIPYRIDAMOLE

Twenty four of the 31 patients developed angina during infusion of dipyridamole. This included the two patients with angiographically normal coronary arteries and normal perfusion images. ST segment depression was evident in only eight patients, all with areas of viable myocardium perfused by collateral vessels.

Discussion

There has been inconclusive evidence to settle the question whether transient defects detected by perfusion scintigraphy with dipyridamole stress represent ischaemia or merely redistribution of blood flow. This study has shown shortening of the duration of monophasic action potentials, characteristic of ischaemia, in areas of myocardium with a reversible perfusion pattern whereas in areas showing a normal perfusion pattern, the duration of the action potential remained unchanged. These data support the view that some degree of ischaemia is usually provoked by selective coronary vasodilation where there is significant flow limiting stenosis. Ischaemia was most evident in areas subtended by occluded arteries with distal collateral circulation from adjacent vessels.

Coronary angiography provides anatomical information with little indication of the pathophysiological importance of coronary stenoses. Perfusion scintigraphy on the other hand, could depict the physiological equivalent of anatomical lesions and therefore be more meaningful clinically. This may hold true for perfusion deficits induced by exercise where there is considerable increase in oxygen demand. In perfusion scintigraphy with dipyridamole stimulus this may not be the case as the predominant mechanism of action is blood flow exceeding demand. In areas of low tracer uptake, blood flow is therefore not reduced in an absolute sense, and such areas should not be considered necessarily ischaemic. Arguments against ischaemia have been based on the relative lack of electrocardiographic changes during dipyridamole infusion occurring in only 20 to 30% of patients.[21] Provocation of angina with dipyridamole is an unreliable indicator of ischaemia since the drug acts through the intermediary adenosine. Adenosine is not only a vasodilator but also a messenger for the sensation of angina.[22] Nevertheless, asynergy of regional wall motion occurs in some patients given intravenous dipyridamole.[10 11 23] This would suggest that flow differences induced by the drug are of sufficient magnitude to provoke myocardial ischaemia leading to transient contractile dysfunction. Our study, with an independent marker, provides good evidence for ischaemia being a significant component of dipyridamole perfusion imaging.

At present, practical methods of identifying localised ischaemia in clinical studies with dipyridamole are the surface electrocardiogram and wall motion asynergy found by any of the imaging techniques. The surface electrocardiogram is relatively insensitive to early myocardial ischaemia and not readily applicable to the interpretation of regional myocardial ischaemia.[18] Although wall motion abnormalities are known accompaniments of early ischaemia, they have been documented in only 50 to 60% of patients with significant coronary artery disease when given a coronary vasodilator.[11 14] This may be due to the relative insensitivity of the currently available imaging techniques to discern small changes that result from early subendocardial myocardial ischaemia. We therefore chose the monophasic action potential signal that records from an area of myocardium about 5 mm in diameter and is therefore suitable for exploring localised electrophysiological events.

Monophasic action potentials recorded from the surface of the myocardium reflect an averaged intracellular action potential for the group of cells beneath the exploring electrode.[24] The amplitude of the signal is less than the intracellular action potential but the duration is reliable for the entire repolarisation phase.[19,25,26] Ischaemia shortens the duration of the action potential by mechanisms that are probably multifactorial.[27] Recordings of monophasic action potentials have been used to monitor ischaemia on both endocardial and epicardial surfaces in animals and in humans.[16,17,28,29] In endocardial studies, the ability of these recordings to detect early changes of ischaemia, which are typically localised to small areas, may be reduced by the conductor properties of blood within the cavity. The exploring electrode is in direct contact with the endocardium. The reference electrode situated 5 mm behind the catheter tip makes contact with the endocardium through the blood in the cavity. Solid angle theory thus predicts that a large area of ischaemia would be relatively undiluted by more distant contact with the surrounding normal myocardium.[30] A small area of ischaemia on the other hand would subtend only a small angle to the reference electrode which might be influenced to a greater extent by the surrounding normal myocardium. In our studies, any error would be an underestimation of the severity of ischaemia.

The shortening of duration of action potentials found is likely to have been a direct result of ischaemia rather than changes related to alterations in catecholamine and potassium concentrations. Neither of these chemicals vary in concentration during the course of the protocol we used (unpublished observations). Dipyridamole would be expected to produce increased myocardial concentrations of adenosine, but adenosine has no significant effect on the duration of ventricular action potentials.[31] Furthermore, in the patients in whom simultaneous recordings were obtained from abnormally and normally perfused areas, the duration of action potentials remained stable throughout the entire 15 minutes of recording in the normally perfused areas.

Most patients in this study were taking β receptor blockers or calcium channel blockers. Neither of these agents are conventionally recognised as influencing the duration of ventricular action potentials.[32] Antianginal medications reduce the ischaemic response to dipyridamole without limiting the hyperemic flow pattern induced by the drug.[14] The number of patients not taking any medication was too few to allow meaningful comparison and assessment of the influence of these drugs on the extent of ischaemia. Nevertheless, we consider it unlikely that either group of medications would have encouraged the development of ischaemia.

The importance of this study is that we have provided strong evidence for the presence of some ischaemia as an integral part of vasodilator myocardial perfusion imaging. Particularly interesting was the striking difference between recordings of action potentials from ischaemic areas showing collateral vessels on angiography compared with areas without collaterals. Collateral circulation in humans develops in response to stimuli arising from prolonged periods of blood flow limitation, and possibly depends on genetically mediated angiogenic factors.[33,34] These vessels are generally considered protective to compromised areas of myocardium. In the context of local coronary vasodilators, however, the reverse would seem to be the case. Such deleterious effects of epicardial collateral vessels have been suggested in previous reports.[35,36] The likely mechanism would be a local coronary steal because of a relative stenosis at the junction of the feeding vessel with the origin of the collaterals.[33]

The high incidence of ischaemia in this study is contrary to previous studies examining the question of ischaemia with coronary vasodilation in coronary artery disease.[15,37,38] These previous studies have focused on electrocardiographic and wall motion abnormalities as indicators of ischaemia. Whereas profound wall motion changes are known to occur a few beats after major coronary artery occlusion in experimental studies, the situation with regard to local subendocardial ischaemia induced by a coronary steal may be different and may not produce discernible wall motion abnormalities. An endocardial to epicardial blood flow steal induced by dipyridamole has been suggested by other investigators[14,39] and is the probable mechanism in the genesis of the ischaemia for areas without collateral vessels in this study. It is nevertheless unlikely that such early ischaemia contributes significantly to the differential uptake of radiotracers in vasodilator perfusion imaging. Most perfusion abnormalities that are commonly seen with vasodilation would be more in keeping with redistribution as the primary mechanism. Ischaemia appears to be provoked in the course of such redistribution of blood flow especially when myocardial viability is dependent upon collateral vessels.

Conclusion

In this study we set out to investigate whether the reversible perfusion defects induced by dipyridamole and seen on myocardial perfusion scintigraphy was associated with the presence of myocardial ischaemia. We would interpret our results as indicating that where there is significant flow limiting coronary stenosis some degree of ischaemia is almost always provoked in the course of redistribution of the coronary flow induced by dipyridamole. Such ischaemia is of greater intensity in areas of viable myocardium with collateral supply. These findings have important implications in the physiological interpretation of a diagnostic test that is rapidly gaining popularity.

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Characteristics of presystolic flow in the superior vena cava: new thoughts on a forgotten sound

S J D Brecker, H B Xiao, M Mbaissouroum, D G Gibson

Abstract

Cross sectional, M mode, and Doppler echocardiography, apexcardiography, and phonocardiography were used to characterise presystolic cardiovascular sounds in three patients with ventricular disease. Although the aetiology was different (dilated cardiomyopathy, primary pulmonary hypertension, and chronic pulmonary thromboembolic disease), in each case the presystolic sound was associated with a rapid change in acceleration of blood and with flow reversal in the superior vena cava, and could only be recorded at the right sternal edge or over the jugular veins. Such flow characteristics may be explained by a raised ventricular end diastolic pressure with reduced compliance. Use of these techniques helps to understand the cause of a previously described but little recognised heart sound, and adds weight to the interpretation of its presence in disease.

Heart sounds may be classified into those originating from the valves, which coincide with the final halt of opening and closing of the valves and are of high frequency, and added ventricular filling sounds, which are of low frequency and comprise the third sound, the atrial or fourth sound, or summation of the two.[1] Such added heart sounds occurring during diastole are important physical findings and often indicate ventricular disease. With non-invasive techniques such as Doppler, phono, and echocardiography, we can study the direction, position, and velocity of blood flow within the heart at the instant an added sound occurs. Such techniques have shown that the onset of a third sound occurs at the time of peak transmitral flow velocity (during rapid filling), whereas a fourth sound usually occurs at the beginning of flow at the start of atrial systole.[2] The mechanisms are thus different from those responsible for the first and second sounds. We now report three cases in which presystolic sounds were identified by phonocardiography. The aetiology in each case was different, yet similar pathophysiological mechanisms have been identified. This added sound has features different from diastolic sounds usually present in patients with ventricular disease, so we analysed the mechanisms responsible.

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Methods

Cross sectional and M mode echocardiograms were taken with the patient in the standard left lateral position with an Advanced Technical Laboratory 860C Imager with a 3·5 MHz mechanical transducer. We recorded Doppler signals with a Doptek Spectrascan and a 2 MHz transducer. Peak transmitral and transtricuspid flow velocities were identified by continuous wave and were recorded in pulsed wave mode with a 3 mm gate and 250 Hz wall filter. Regurgitant flow was identified and recorded in continuous mode. Apexcardiograms were recorded from the point of maximal impulse by a Cambridge Instruments transducer with a time constant of four seconds. Phonocardiograms were recorded from a Leatham microphone with a low frequency filter. Apexcardiograms, M mode echocardiograms, and Doppler traces were recorded separately with simultaneous electrocardiogram and phonocardiogram on a Honeywell (Ecoline 22) strip chart recorder at a paper speed of 10 cm/s.

Case reports

PATIENT 1

A 46 year old woman with previous good health presented with chest pain and breathlessness. Physical examination revealed tachycardia, raised venous pressure (20 cm above the sternal angle), ankle oedema, and cardiomegaly. Her chest *x* ray film showed pulmonary oedema, although her electrocardiogram and cardiac enzyme concentrations were normal. A diagnosis of viral myopericarditis was made during a prolonged hospital admission, and she was discharged on diuretics and angiotensin converting enzyme inhibitors. She was readmitted four months later with increasingly severe dyspnoea, orthopnoea, and ankle swelling. Pansystolic murmurs were audible at the apex and lower left sternal edge. Chest *x* ray film showed an enlarged cardiac shadow with pulmonary venous congestion, and her electrocardiogram remained unchanged from the previous recording with a heart rate of 120 and PR interval of 0·16 s. She was referred for echocardiographic assessment. This showed biventricular enlargement with global hypokinesis. No convincing added sound could be heard with phonocardiography from the left sternal edge. An unimpressive low frequency deflection was present at the peak of rapid filling, but after the start of the succeeding P wave (fig

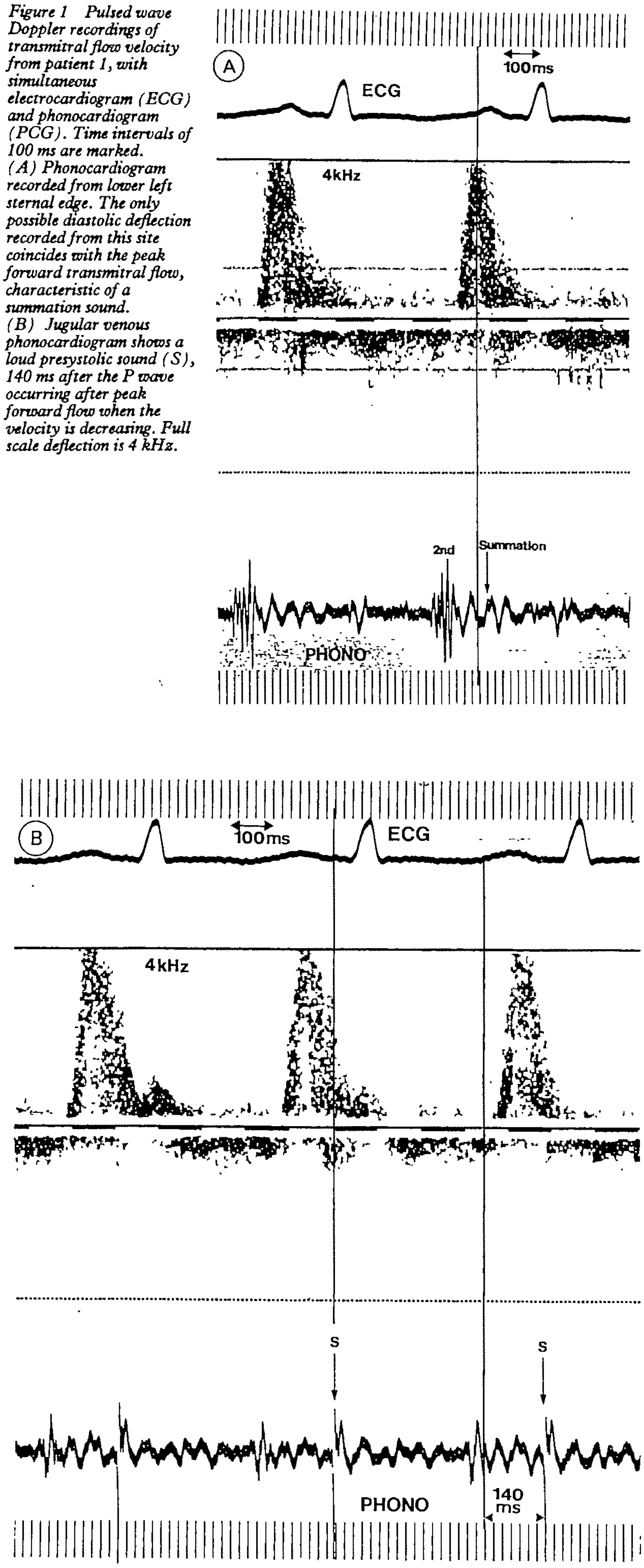

Figure 1 Pulsed wave Doppler recordings of transmitral flow velocity from patient 1, with simultaneous electrocardiogram (ECG) and phonocardiogram (PCG). Time intervals of 100 ms are marked. (A) Phonocardiogram recorded from lower left sternal edge. The only possible diastolic deflection recorded from this site coincides with the peak forward transmitral flow, characteristic of a summation sound. (B) Jugular venous phonocardiogram shows a loud presystolic sound (S), 140 ms after the P wave occurring after peak forward flow when the velocity is decreasing. Full scale deflection is 4 kHz.

1A). The only possible explanation of this would be a summation sound. No other added sound was recorded from this site, but on the jugular venous phonocardiogram, 140 ms after the start of the P wave, a second, loud high frequency vibration was present (fig 1B). This sound was localised to an area at the base of the neck and upper right sternal edge. It could not be recorded by placing the microphone lower down the sternal edge or at the apex. The short diastolic filling time, localised nature, and timing in relation to the P wave made it unlikely to be a fourth heart sound, so a detailed Doppler, echo, and phono cardiographic study was performed to identify its origin.

The first and second heart sounds occurred normally in association with mitral and aortic closure identified from the corresponding echograms. Mitral and tricuspid regurgitation were present, limiting the time available for filling of the left ventricle to 220 ms, and the right to 260 ms. On the transmitral Doppler recording a single peak of forward flow was identified and the only possible added sound recordable from the left sternal edge coincided with the peak velocity of left ventricular inflow, characteristic of a summation sound (fig 1A). The sound under study occurred 90 ms after this and 40 ms after peak forward tricuspid flow while the velocity of atrioventricular flow on both sides of the heart was steadily decreasing. Premature closure of the tricuspid valve[3] was excluded by showing normal timing on the echocardiogram of the tricuspid valve, co-incident with the first heart sound. As the maximal amplitude of the sound was recorded with the transducer placed beneath the right clavicle, we considered the possibility of the origin of the sound being within the superior vena cava. We therefore recorded pulsed wave Doppler signals from the right supraclavicular fossa directed towards the right atrium (fig 2). A simultaneous jugular venous pulse recording showed that the "x" descent was shallow, but the "y" descent was dominant and deep, indicating predominant early diastolic antegrade flow into the right atrium characteristic of a restrictive filling pattern. Also the apexcardiogram was strongly suggestive of restricted ventricular filling. Diastolic downward flow was recorded from the superior vena cava to the right atrium on Doppler. On the spectral display a rapid halt to forward flow could be seen with subsequent flow reversal (peak forward velocity 0·5 m/s; acceleration in a retrograde direction 7·7 m/s^2 = 0·79 g) occurring before ventricular systole, with retrograde flow from the right atrium towards the superior vena cava. The start of the high-pitched added sound occurred at the time of peak velocity of inflow to the right atrium and coincided with abrupt deceleration.

PATIENT 2

A 29 year old woman with primary pulmonary hypertension was referred for assessment for heart lung transplantation. She had been born a twin by caesarean section. At school she had been breathless on mild exertion and had

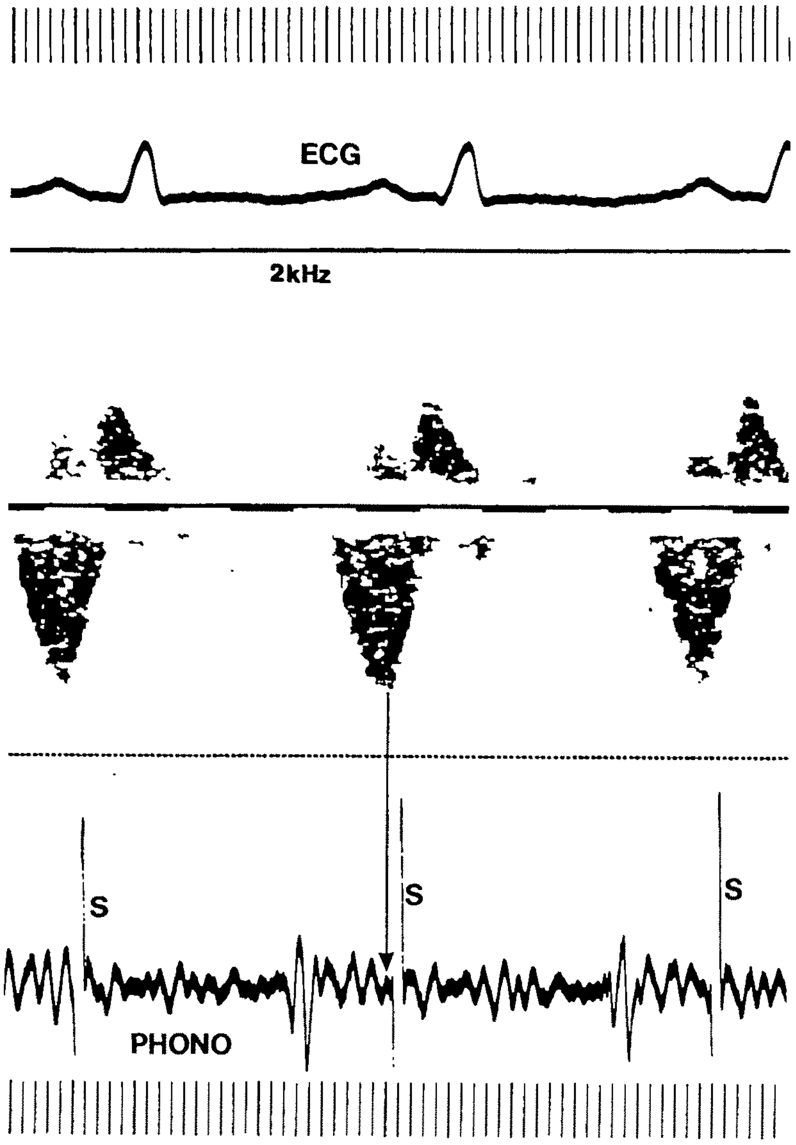

Figure 2 Pulsed wave Doppler flow of the superior vena cava recorded from the right supraclavicular fossa directed towards the right atrium from patient 1. Simultaneous electrocardiogram (ECG) and jugular venous phonocardiogram (PCG) are displayed. Loud presystolic "superior vena cava sound" (S), the start of which coincides with the peak velocity into right atrium at a point of abrupt deceleration. Full scale deflection is 2 kHz.

avoided strenuous activities. Symptoms progressed and cyanosis was noted. After cardiac catheterisation at another hospital, a diagnosis of primary pulmonary hypertension had been made and she was referred for assessment and consideration for heart-lung transplantation. On examination she was centrally cyanosed and her pulse was 80 beats per minute and regular with a normal volume and waveform. The venous pressure was raised to 20 cm with a giant "a" wave clearly visible (fig 3). Blood pressure was 110/70 mm Hg, the right ventricular impulse was prominent, and on auscultation, a gallop rhythm together with a soft pansystolic murmur were audible at the apex. The pulmonary component of the second heart sound was accentuated. The electrocardiogram showed right axis deviation and chest *x* ray film showed enlarged pulmonary arteries with peripheral pruning. At cardiac catheterisation, pulmonary artery pressure was recorded as 170/110 mm Hg. A diagnosis of primary pulmonary hypertension with a patent foramen ovale was made.

Echocardiography showed a small left ventricular cavity and a hypertrophied and mildly dilated right ventricle. Tricuspid regurgitation was present with a peak right ventricular atrial gradient of 110 mm Hg being recorded. Phonocardiography showed a presystolic sound recorded over the upper right sternal edge 130 ms after the start of the P wave. The transtricuspid Doppler signal (fig 4A) showed that forward atrioventricular flow had ceased and eliminated the possibility of this being a fourth heart sound. Thus despite electrical and mechanical evidence of atrial activity no atrial transtricuspid flow could be detected, implying a fixed end diastolic right ventricular volume into which no further filling could occur. Superior vena caval flow was examined with Doppler from the supraclavicular fossa (fig 4B). Flow reversal could be detected, with clear retrograde flow from right atrium to superior vena cava. The peak velocity of this retrograde flow (0·55 m/s, acceleration, $9{\cdot}6\ m/s^2 = 0{\cdot}98\ g$) occurred 130 ms after the beginning of the P wave. The start of the added presystolic sound coincided with the peak retrograde velocity, when the acceleration changed to deceleration.

PATIENT 3

A 57 year old West Indian woman with chronic pulmonary thromboembolic disease was referred for assessment because of progressive dyspnoea for eighteen months. Her pulse rate was 90 beats per minute and regular and blood pressure was 160/100 mm Hg. The venous pressure was raised with a prominent "a" wave visible. A prominent right ventricular impulse was palpable, a fourth heart sound was audible, and the pulmonary component of the second sound was prominent. Chest *x* ray film showed enlarged proximal pulmonary arteries and an enlarged cardiac shadow. The electrocardiogram showed right axis deviation, P pulmonale, and inverted T waves over leads V1-V4. At cardiac catheterisation the following pressures were recorded (mm Hg): right atrium, a 17, mean 13; right ventricle 75/14; main pulmonary artery 70/30, mean 45. Pulmonary angiography showed filling defects in the right main and both lower lobe pulmonary arteries.

Echocardiography showed the right ventricle to be dilated with reversal of septal motion. Prolonged tricuspid regurgitation shortened the right sided filling time to less than 200 ms. A single peak was present on the Doppler recording of forward tricuspid flow, the start of which coincided with a fourth heart sound recorded at the right sternal edge. A louder presystolic sound was recorded over the right jugular veins. Simultaneous jugular phonocardiography and recording of superior vena caval flow on Doppler (fig 5) showed that this presystolic sound coincided with the start of retrograde flow in the superior vena cava after atrial systole (peak retrograde velocity 0·34 m/s; acceleration $15{\cdot}4\ m/s^2 = 1{\cdot}57\ g$).

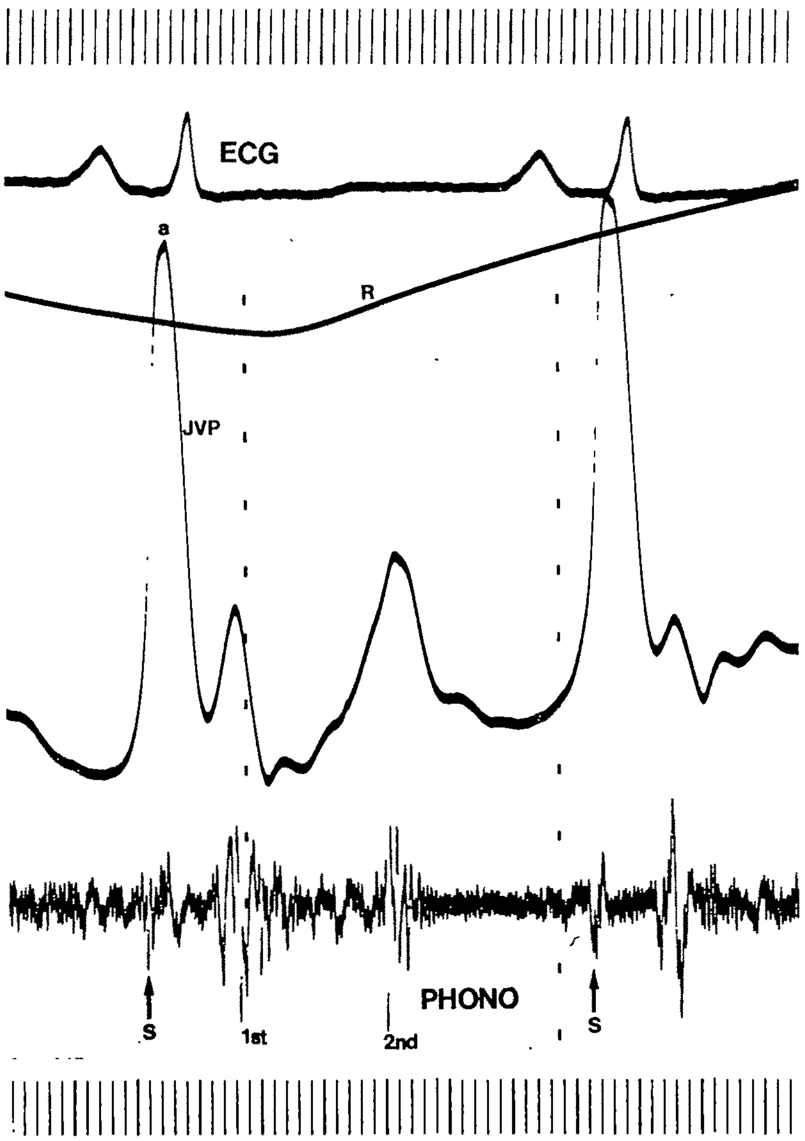

Figure 3 Recording of jugular venous pulse (JVP) from patient 2, with simultaneous electrocardiogram (ECG), phonocardiogram (PCG), and respiratory trace (R), from patient 2. Giant "a" wave coincides with presystolic sound (S). First and second heart sounds are indicated.

Discussion

The invention of the stethoscope by Laennec in 1826 gave physicians the opportunity to use clinical skills in the diagnosis of cardiac disease.[4] Within 10 years of this, controversy developed about the physical processes underlying the generation of heart sounds. The first and second heart sounds are generally thought to arise from closure of the atrioventricular and semilunar valves.[1] Diastolic sounds seem to be more closely related to ventricular filling, and may be right or left sided. Physiological and pathological third sounds are associated with the peak of rapid filling at the time of peak velocity of inflow. Studies with a miniature accelerometer of ventricular wall dynamics in dogs, have shown that the third sound is simultaneous with sudden reduced acceleration.[5] Similar techniques have been applied to humans with third sounds, and this work supports the concept that the third sound is produced by a sudden intrinsic limitation of longitudinal expansion of the left ventricular wall during early diastole.[6] Fourth sounds usually occur at the beginning of atrioventricular flow after atrial systole, when acceleration of blood starts.[2] Apart from mitral and tricuspid opening snaps, the only other commonly recognised diastolic sound is a pericardial knock. This is an early diastolic sound heard along the left sternal edge in constrictive pericarditis, and corresponds to the sudden end of ventricular filling and the premature diastolic plateau of the ventricular volume curve.[7] It occurs simultaneously with the nadir of the "y" descent on the recording of jugular venous pressure. We have already published a case report of a sound during isovolumic relaxation due to intracavity flow.[8] This sound occurred at the time of peak flow velocity when acceleration had stopped and deceleration had started. Thus the general mechanism of diastolic sound production seems to be related to the dissipation of energy associated with sudden changes in acceleration.

The presystolic sounds in our patients had none of the usual characteristics by which we recognise common diastolic sounds. In case 1 the sound occurred after the peak forward transmitral flow and was not associated with atrial systolic flow into the ventricle. We confirmed that it was not due to premature tricuspid closure[3] (the normal PR interval made this unlikely). Premature mitral closure has been described in a patient with aortic regurgitation and first degree heart block.[9] Again, examination of the Doppler trace and mitral echogram confirmed that this could not be the explanation. The other unusual feature was the specific localisation over which the sound could be recorded. This was limited to an area beneath the right clavicle in the parasternal region. The diastolic sound in this patient corresponded in time to a change in acceleration associated with subsequent flow reversal in the Doppler recording from the superior vena cava. Acceleration of blood had ceased and deceleration had started, and blood flow in the superior vena cava subsequently became retrograde. The sudden change of acceleration to deceleration requires the operation of a force and dissipation of energy that appears as mechanical vibrations generating the added sound and may occasionally even be palpable in the venous pulse. The change in acceleration responsible for the added sound in this case is analogous to that responsible for a third heart sound, but comes from different circulatory structures. The question arises why such a change in acceleration and abnormal flow reversal should occur. This patient's apex cardiogram strongly suggested restricted ventricular filling. The patient's previous myocarditis had progressed to cause substantial ventricular impairment and it seems reasonable that such a ventricle could display restrictive properties. Hence, during rapid early diastolic filling a point is reached where atrioventricular blood flow rapidly decelerates yet venous return from the great veins continues. In this situation subsequent retrograde flow into the superior vena cava would occur. Possibly the start of atrial systole

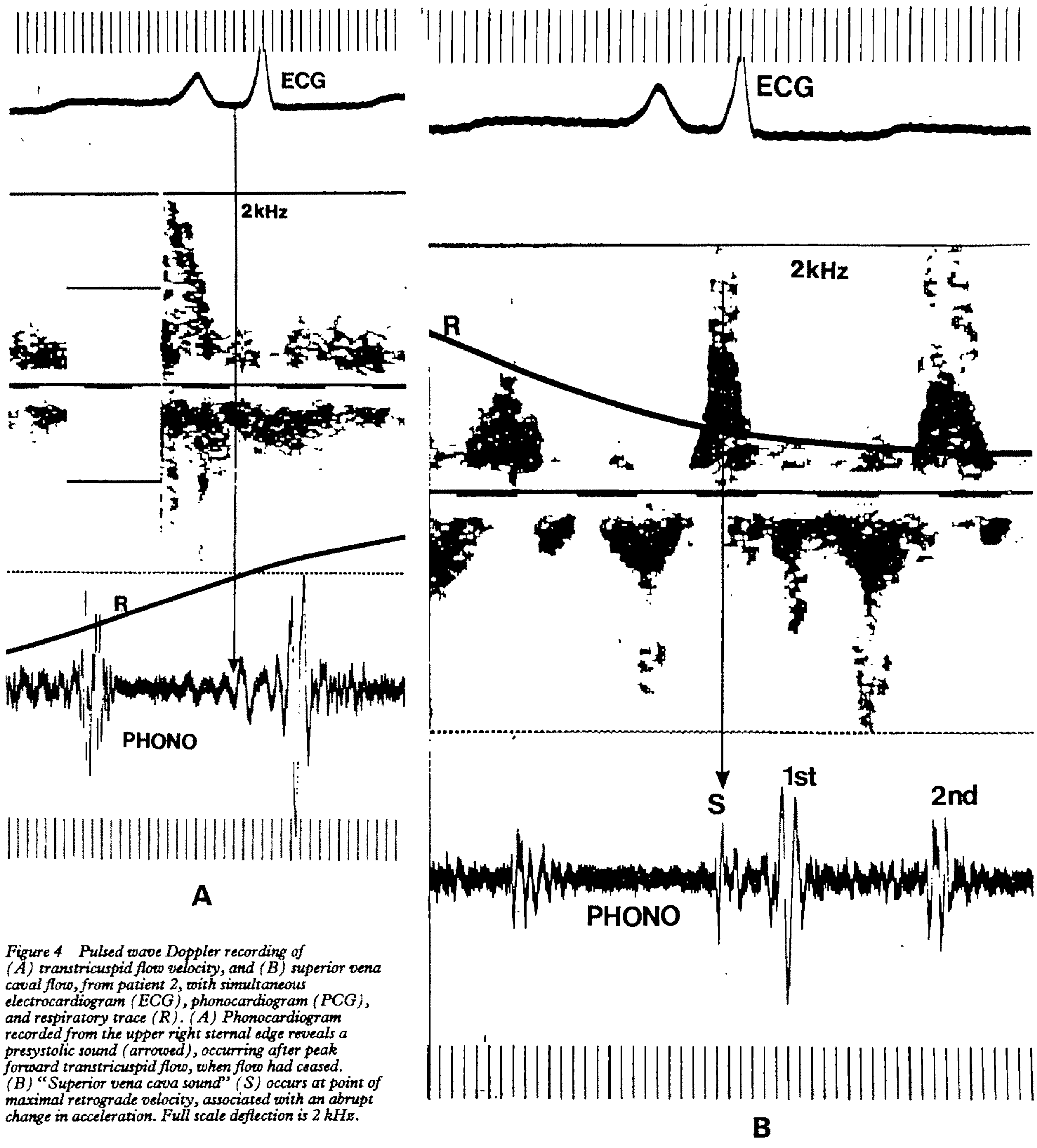

Figure 4 Pulsed wave Doppler recording of (A) transtricuspid flow velocity, and (B) superior vena caval flow, from patient 2, with simultaneous electrocardiogram (ECG), phonocardiogram (PCG), and respiratory trace (R). (A) Phonocardiogram recorded from the upper right sternal edge reveals a presystolic sound (arrowed), occurring after peak forward transtricuspid flow, when flow had ceased. (B) "Superior vena cava sound" (S) occurs at point of maximal retrograde velocity, associated with an abrupt change in acceleration. Full scale deflection is 2 kHz.

would increase the pressure gradient underlying this retrograde flow. Normal venous compliance dictates a considerable phase delay between flow and increase in pressure. In this case the flow and pressure changes in the superior vena cava were in phase, indicative of reduction in compliance or increased stiffness of the venous system. This would be expected when the venous pressure itself is greatly raised and provides further support for the venous origin of the sound under discussion. The high-pitched nature of the sound might be a measure of the stiffness of the vein.

In our second case the timing of the added sound was later and occurred 130 ms after the start of the P wave. At first sight, this has the characteristics of a fourth heart sound, being coincident with the "a" wave. Forward tricuspid flow and hence ventricular filling had stopped at this point, however, making the possibility of atrioventricular origin of this sound unlikely. In this case the sound followed a rapid reversal of flow in the superior vena cava, occurring at the point of peak velocity of flow away from the atrium. The magnitude of the change in acceleration was greatest in the retrograde direction, which may explain the difference in timing from the first case. In both cases 1 and 2, however, the change from acceleration to deceleration implies a change in

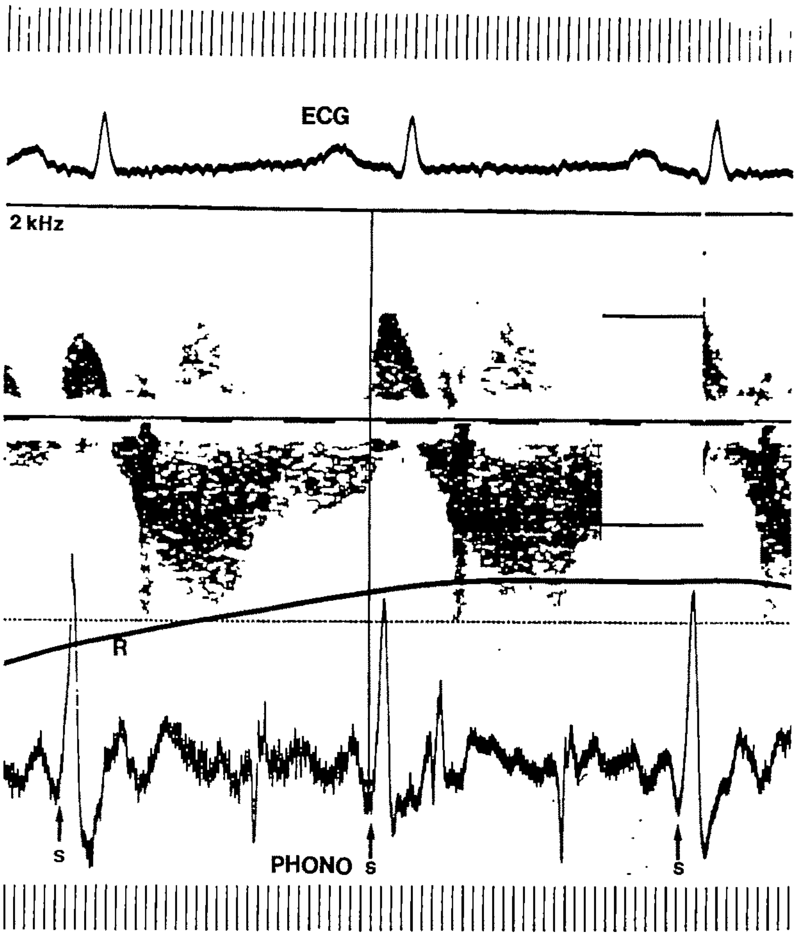

Figure 5 Pulsed wave Doppler recording of superior vena caval flow from patient 3, with simultaneous electrocardiogram (ECG), jugular phonocardiogram (PCG) and respiratory trace (R). The presystolic sound (S) occurs at the start of retrograde flow in the superior vena cava, again associated with a change in acceleration. Full scale deflection is 2 kHz.

the direction of the force acting on the blood.

In the third case the sound was only recorded directly over the jugular veins. Atrial systole caused both antegrade flow into the right ventricle (with a fourth heart sound recorded over the lower left sternal edge), and rapid reversal of flow in the superior vena cava. The sound over the jugular veins occurred 120 ms after the P wave and coincided with the start of acceleration and retrograde flow.

The concept of presystolic sounds of venous origin is not new. In 1908, Sir James Mackenzie heard "a clear, sharp sound preceding the first sound" over the jugular veins of a patient with tricuspid stenosis.[10] He concluded that contraction of a hypertrophied right atrium "sent back a large wave into the jugular, and with such force that it caused the valves in the jugular and subclavian veins to close with a snap." Groedel and Miller recorded jugular venous phonocardiograms describing presystolic sounds interpreted as being of venous origin—" . . . the great veins may be important as sound conductors, even in the direction opposite to the flow of blood."[11] Eight years later Dock described the recording of loud sounds during atrial systole over the jugular veins of patients with raised right atrial pressure.[12] Twelve cases were described with various pathological conditions. In two cases the diagnosis was tricuspid stenosis, and it was postulated that reflux of blood into the great veins set up vibration in the tensed veins so causing a loud sound. This sound was not audible, however, below the clavicle. The postulated mechanism was violent retrograde flow at the height of atrial systole associated with high right ventricular end diastolic pressure, or tricuspid stenosis. We can find no reference to these sounds in publications since 1956, although our experience suggests that they are not uncommon. In our patients we postulate a similar mechanism to that suggested by Dock, and have been able to show the sudden change in acceleration of blood associated with flow reversal. We thus extend Dock's ideas by suggesting that it is the dissipation of energy associated with this sudden acceleration change that generates vibrations within the great veins and hence the sound. In the first two cases, the sound can be shown to occur at a time of peak velocity, when acceleration has ceased. In the first case this occurred at the point of peak forward velocity of flow from the superior vena cava to the right atrium. In the second case the sound coincided with peak reverse velocity from the right atrium to the superior vena cava. In our third case the sound occurred at the start of rapid acceleration of blood in a retrograde fashion, more in keeping with the mechanism of a classical fourth heart sound. Thus this previously described but little recognised class of sound can be shown to have the same basic mechanisms as classical ventricular third and fourth heart sounds.

We believe a suitable name for this added sound is a "superior vena cava sound." Alternative titles such as "fifth sound" may be confusing and "presystolic sound" tells us little about the mechanism producing it. It may be that different classes of this sound will be further defined according to their precise time relations to the flow reversal—for example, "forward flow," "reverse flow," or "acceleration" sounds. Nevertheless, for the time being the term "superior vena cava sound" seems attractive and defines the site of flow reversal.

Phonocardiography has become less popular in recent years. Nevertheless, its use with Doppler and echocardiography makes it possible to describe and explain a class of heart sound, virtually unrecognised since its description by Mackenzie over 80 years ago. Physicians should be alert to the presence of such sounds, as with increased understanding of their genesis, such physical signs may continue to provide valuable information about ventricular physiology.

We thank Dr Martin St John Sutton, Dr Jane Somerville, and Dr Paul Oldershaw for allowing us to discuss their patients in the above case reports.

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ABSTRACTS IN CARDIOLOGY

Prediction of sudden death in hypertrophic cardiomyopathy

Abnormalities of heavy chain myosin account for perhaps 50% of hypertrophic cardiomyopathy (HCM). It now seems that the site and nature of the aminoacid change influence survival. Why should this be? One possibility is that the substitutions interfere to a different degree in myofibrillary organisation within the myocyte. It is probably significant that the substitution leading to a change in charge has the greatest deleterious effect on survival. Abnormal myofibrillary organisation probably leads in turn to misshapen cells and abnormalities in cell to cell organisation producing disarray and an ideal substrate for arrhythmias. Family history remains a cheap way of identifying those with HCM at high risk of sudden premature death but a good case can be made for determining the exact gene abnormality. The understanding of how HCM affects myocyte structure will be further forwarded when the other genes unrelated to heavy chain myosin are discovered. These are exciting times for those interested in HCM.

M J DAVIES

Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy

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Abstract Background—Familial hypertrophic cardiomyopathy is characterized by a variable degree of myocardial hypertrophy and a wide range of symptoms. Different mutations in the β cardiac myosin heavy-chain gene have been identified in three affected families. However, neither the proportion of cases attributable to myosin mutations nor the effects of different mutations on clinical outcome are known.

Methods—Using a ribonuclease protection assay, we screened the β cardiac myosin heavy-chain genes of probands from 25 unrelated families with familial hypertrophic cardiomyopathy; this assay is a sensitive method for detecting the presence and location of mutations. We further defined the mutations by analyzing their nucleotide sequences. The clinical features of the disease were compared in families with various myosin mutations.

Results—Seven mutations in the β cardiac myosin heavy-chain gene were identified in 12 of the 25 families. All were missense mutations (i.e., causing the substitution of a single amino acid) clustered in the head and headrod junction regions of the molecule. Six mutations resulted in a change in the charge of the amino acid. Patients with mutations that changed the charge of the altered amino acid (such as that from arginine to glutamine at nucleotide 403 or from arginine to cysteine at nucleotide 453) had a significantly shorter life expectancy (mean age at death, 33 years), whereas patients with the one mutation that did not produce a change in charge (Val606Met) had nearly normal survival. However, patients with different mutations did not differ appreciably in their clinical manifestations of familial hypertrophic cardiomyopathy.

Conclusions—Different missense mutations in the β cardiac myosin heavy-chain gene can be identified in approximately 50 percent of families with hypertrophic cardiomyopathy. In those families, a definite genetic diagnosis can be made in all members. Since the location of a mutation or its DNA-sequence alteration (or both) appears to influence survival, we suggest that the precise definition of the disease-causing mutation can provide important prognostic information about affected members (*N Engl J Med* 1992;326:1108–14.)

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Plasma concentration of atrial natriuretic peptide at admission and risk of cardiac death in patients with acute myocardial infarction

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Abstract

***Objective*—To compare the concentration of plasma atrial natriuretic peptide in patients with acute myocardial infarction with a healthy population and to determine whether a raised concentration of plasma atrial natriuretic peptide at admission was a predictor of mortality after acute myocardial infarction.**

***Design*—Patients with acute myocardial infarction were divided into a group with no congestion (class I) and a group with congestion (class II-IV) according to their highest Killip classification in the first 24 hours after infarction. The concentration of plasma atrial natriuretic peptide was measured at admission. On the basis of the concentration of atrial natriuretic peptide measured in the healthy population, patients were separated into two groups: a group with a high (>200 pg/ml) and a group with a low concentration of atrial natriuretic peptide (≤200 pg/ml). The patients were followed for three years.**

***Patients*—55 patients admitted to the coronary care unit within 12 hours of the appearance of symptoms of acute myocardial infarction were compared with 51 healthy individuals.**

***Main outcome measures*—Plasma atrial natriuretic pepetide, Killip class, mortality.**

***Results*—The patients had significantly higher concentrations of atrial natriuretic peptide than the healthy controls. Furthermore, patients with congestion had a significantly higher concentration of atrial natriuretic peptide than the uncongested group of patients. Total mortality was 34·5%. In the group with a low concentration of atrial natriuretic peptide the mortality was only 13·6%, whereas mortality was significantly higher (48·5%) in the group with a high concentration.**

***Conclusions*—The measurement of atrial natriuretic peptide separated the patients into low and high risk groups after acute myocardial infarction.**

During the past 30 years the hospital stay for uncomplicated acute myocardial infarction has progressively shortened.[1] To identify those patients at high risk of an early death after acute myocardial infarction many risk factors have been evaluated including the emergency electrocardiogram,[2] early exercise test,[3] predischarge maximal exercise test,[4] the concentration of creatine kinase,[5] and haemodynamic measurements.[6] Since the establishment of coronary care units about 20 years ago, the number of deaths primarily attributed to cardiac arrhythmias has decreased and clinical heart failure, or more accurately left ventricular impairment, has emerged as the prime factor responsible for most deaths after acute myocardial infarction.[7–9]

The concentration of plasma atrial natriuretic peptide is reported to be higher in patients with left ventricular dysfunction and to correlate well with the function of the left ventricle in both chronic[10–12] and acute heart disease.[13]

We have compared the concentration of plasma atrial natriuretic peptide in patients with acute myocardial infarction with that in a group of healthy controls. Because left ventricular dysfunction determines mortality after myocardial infarction,[14] we wanted to examine whether a raised concentration of atrial natriuretic peptide at admission predicted mortality after acute myocardial infarction and could be used as an easily measured indicator of left ventricular function.

Patients and methods

From 1 April 1987 to 31 March 1988, 191 patients were admitted to our hospital with acute myocardial infarction. In this study we included all patients admitted to the coronary care unit who fulfilled the following criteria: (*a*) infarction diagnosed according to the criteria of the World Health Organisation,[15] (*b*) clinical evaluation and blood samples taken within 12 hours of the onset of symptoms, (*c*) no vasoactive drugs given at admission before the blood samples were taken, (*d*) serum creatinine concentration <200 μmol/l at admission, (*e*) no history of chronic liver disease, (*f*) no permanent or temporary pacemaker treatment, (*g*) no resuscitation before admission, (*h*) informed consent. Patients were excluded if they did not meet the inclusion criteria. The patients we studied were followed up to determine mortality. The study was approved by the local ethics committee.

Blood samples were collected at admission from a cubital vein into EDTA-coated tubes containing aprotinin 500 IU/ml and kept in an ice bath. The plasma was centrifuged within an hour and then stored at −20°C until analysis. We used a highly specific and reproducible radioimmunoassay from INC, Holland that included plasma extraction before analysis.[16] The kit was tested in our laboratory: intra and inter assay variation was 5% and 10% respectively. Recovery of added atrial natriuretic peptide was 99% (sensitivity, 0·8 pg/tube = 4 pg/ml plasma).

A normal range of atrial natriuretic peptide was established in 51 healthy controls (20 women) (mean age 54·9, range 27–82 years). They were not taking any medication, had no history of chronic liver or heart disease, and had a serum creatinine concentration of < 200 μmol/l. The concentration of plasma atrial natriuretic peptide ranged from 25 to 200 pg/ml (mean (SD) 83 (38·4) pg/ml). On the basis of the concentration of atrial natriuretic peptide in the healthy controls we divided the patients with acute myocardial infarction into two groups: one group with low (≤200 pg/ml) and one with a high atrial natriuretic peptide concentration (>200 pg/ml).

Patients with acute myocardial infarction were divided into an uncongested (Killip class I) group and congested (Killip class II–IV) group in order to compare the concentration of atrial natriuretic peptide in the two groups.[17] Patients were classified according to the highest Killip class attained during the first 24 hours after myocardial infarction. The patients were classified by two of the authors (JS and KA-N) without knowing the concentration of plasma atrial natriuretic peptide.

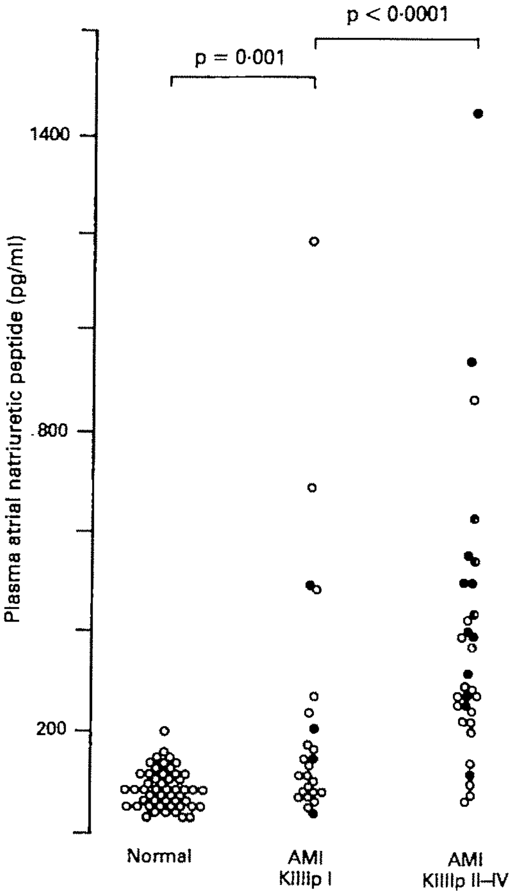

Figure 1 Concentration of plasma atrial natriuretic peptide in 51 healthy controls compared with 24 patients in Killip class I and 31 patients in Killip class II-IV with acute myocardial infarction (AMI). Solid circles indicate patients who died.

STATISTICAL ANALYSIS

We used the two-sample rank sum test (Mann-Whitney test). The differences in survival curves were calculated by a log rank test.[18] Dichotomised data were analysed by a χ^2 test. We compared the concentration of atrial natriuretic peptide in healthy controls and patients by analysis of covariance after adjusting for age. We used the Cox model for regression in survival to analyse the concentration of atrial natriuretic peptide as a continuous value. The relative risk of death for a given increase in the concentration of atrial natriuretic peptide was calculated from the slope of the regression line.[19]

Results

We studied 55 patients (15 women) admitted to the coronary care unit with acute myocardial infarction. They were all admitted within 12 hours (median time 3·0 hours) from the onset of symptoms of myocardial infarction. Atrial natriuretic peptide was significantly higher in the patients with acute myocardial infarction than in the healthy controls ($p < 0·00001$). In the first 24 hours after infarction 24 patients were in Killip class I (uncongested) and 31 patients were in Killip class II–IV (congested). Table 1 shows the age, mean concentration of atrial natriuretic peptide, and sex in the controls and patients. In the controls there was a significant correlation between age and atrial natriuretic peptide (regression line for atrial natriuretic peptide (pg/ml) = 1·32 × age (years) + 9·8; $r = 0·53$, $p = <0·001$). The concentration of atrial natriuretic peptide was similar in men and women ($p = 0·19$). The concentration of atrial natriuretic peptide in the uncongested patients (Killip class I) was significantly different from that in the controls and in the congested patients (Killip class II–IV) with acute myocardial infarction (fig 1). Three (43%) of the seven uncongested patients with a high concentration of atrial natriuretic peptide at admission became congested 24–48 hours after infarction, compared with three (18%) of the 17 uncongested patients in whom the concentration of atrial natriuretic peptide was low at admission. This difference was not statistically significant.

Table 1 Mean values for age, sex, and atrial natriuretic peptide in healthy controls and patients with acute myocardial infarction

	Healthy controls (n = 51)	*Patients Killip class I (n = 24)*	*Patients Killip class II-IV (n = 31)*
Age (mean (SD))	54·9 (15·6)	61·7 (11·7)	66·1 (8·7)
Females (%)	20 (39)	7 (29)	8 (26)
ANP (pg/ml)	82·9	221·3	390·0

ANP, atrial natriuretic peptide.

The mean observation time for all patients was 1094 days (range 929–1273 days). Nineteen

Table 2 Basic characteristics of the patients

	Deaths (n = 19)	*Survivors (n = 36)*	*p Value*
Age (mean (SD))	68 (11·2)	62 (9·2)	0·052
Women (%)	6 (32)	9 (25)	0·83
Pre-existing factors:			
AMI (%)	6 (32)	4 (11)	0·13
Angina pectoris (%)	11 (58)	11 (31)	0·09
Hypertension (%)	10 (53)	8 (22)	0·047
Atrial flutter (%)	1	0	
Congestion (%)	3 (16)	3 (8)	0·7

patients died during the follow up period. Table 2 shows the salient clinical characteristics of those who died and those who survived.

Figure 2 shows the relations between the groups with low (≤200 pg/ml) and high (above 200 pg/ml) values of atrial natriuretic peptide and survival in the follow up period. Three (13·6%) of 22 patients in the group with a low value of atrial natriuretic peptide died. Mortality was significantly higher 16/33 (48·5%) in the group with a high value.

Figure 2 also shows the relation between the highest Killip classification in the first 24 hours after myocardial infarction and survival. Four (16·7%) of the 24 uncongested patients in Killip class I died compared with 15 (48·4%) of 31 patients with congestion (Killip class II–IV). We used the Cox model for regression in survival to avoid arbitrary cut off points between groups and to use the concentration of atrial natriuretic peptide as a continuous value. This gave a relative risk of 1·7 for death for a doubling of the concentration of atrial natriuretic peptide (p = 0·0056).

When both plasma atrial natriuretic peptide and the Killip classification were included as covariates they did not explain significantly more of the survival rates than the values of atrial natriuretic peptide alone, but the values of atrial natriuretic peptide gave more information than the Killip values alone.

Discussion

Atrial natriuretic peptide was higher in the patients (both uncongested and congested) with acute myocardial infarction than in the healthy controls. We found that the concentration of plasma atrial natriuretic peptide immediately after infarction was significantly higher in congested patients than in patients without congestion and that the concentration of atrial natriuretic peptide of both groups was higher than in healthy controls. It seems to be the severity of the left ventricular dysfunction rather than the degree of myocardial ischaemia that determines the concentration of atrial natriuretic peptide. During percutaneous transluminal coronary angioplasty, which always causes ischaemia of a part of the heart muscle, the concentration of atrial natriuretic peptide was higher in patients in whom pulmonary capillary wedge pressure increased whereas it remained normal in patients in whom it did not increase. Furthermore, myocardial ischaemia provoked by dynamic exercise did not in itself increase the concentration of atrial natriuretic peptide in plasma.[20] There was a good correlation between atrial natriuretic peptide and capillary wedge pressure in uncongested patients during dynamic exercise 10 hours after the onset of symptoms of acute myocardial infarction.[13]

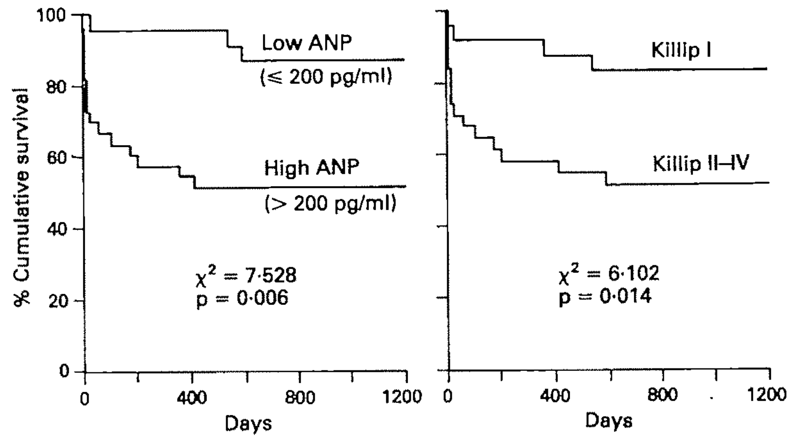

Figure 2 Relation between plasma atrial natriuretic peptide (ANP) and cumulative survival (left) and relation of Killip classification and cumulative survival (right).

In a rat model of myocardial infarction neither atrial natriuretic peptide nor the left ventricular end diastolic pressure correlated linearly with infarct size, whereas there was a good linear correlation between atrial natriuretic peptide and left ventricular end diastolic pressure ($r = 0·89$, $p < 0·001$) during volume expansion.[21] An increased concentration of atrial natriuretic peptide is likely to aggravate congestive heart failure because intravenous administration of atrial natriuretic peptide reduced blood pressure and increased haemoconcentration in healthy individuals.[22] Because atrial natriuretic peptide increases transcapillary water shifts by altering vascular permeability, it has been proposed that a high concentration of atrial natriuretic peptide could contribute to pulmonary oedema in left sided myocardial disease and valve disease. This does not seem to be true of chronic heart failure where "acute" atrial natriuretic peptide infusion in several studies was associated with potentially beneficial renal, endocrine, and haemodynamic effects.[23,24] The vasodilatation and decrease in systemic vascular resistance that have been demonstrated could explain the harmful effect of atrial natriuretic peptide in healthy individuals. We know of no studies of the infusion of atrial natriuretic peptide in patients with acute heart failure.

We found a weak but significant increase in atrial natriuretic peptide with age in our healthy controls. Others, however, found no correlation in 124 younger healthy blood donors.[25] This might be because of differences in methods: we and others[26,27] found a positive correlation in healthy controls at all ages. It has been suggested that this positive correlation with age reflects increasing morbidity from other causes. To ensure that we used a cut off value that was independent of age we chose the highest value in the healthy controls (200 pg/ml).

Plasma atrial natriuretic peptide has already been used as a prognostic indicator in chronic heart failure, where in 102 patients those with concentrations above the median concentration of atrial natriuretic peptide had a significantly lower two year survival rate than those with a lower concentration.[28]

We found that the Killip classification in the first 24 hours after myocardial infarction was a reliable prognostic indicator. All but four of those who died were in clinical heart failure at this time. This accords with the results of a study by Califf *et al*, who found that mortality in patients with coronary disease was strongly associated with left ventricular dysfunction. The detection of ventricular arrhythmias during a 24 hour monitoring period gave no further information on the prognosis if the haemodynamic indices were known.[29] The methods of assessing left ventricular dysfunction differ from one investigation to another, but in all mortality was associated with the degree of heart failure. A combination of physiological markers such as low left ventricular ejection fraction measured by radionuclide ventriculography, clinical heart failure, and radiological heart failure enhances the reliability of evidence of heart failure as a marker of mortality after acute myocardial infarction.[30] Pulmonary capillary wedge pressure measured at admission to the hospital gives a better indication of subsequent mortality than later measurements.[31] This might explain why radionuclide ventriculography performed 10 days after infarction in 39 patients with overt pulmonary oedema (Killip class III) was unable to predict the larger mortality in patients with an ejection fraction lower than 0·45 than in patients with a larger ejection fraction. The correlation between ejection fraction and pulmonary capillary wedge pressure was poor because pulmonary capillary wedge pressure in the two groups did not differ.[32] The difficulties in estimating heart failure several days after an acute myocardial infarction could be caused by treatment given soon after admission. Compared with other methods of predicting mortality atrial natriuretic peptide has the advantage that the blood sample can be drawn immediately at admission (day or night) by regular staff. The Killip classification is also a simple, reliable and easy way to predict mortality after a myocardial infarction. We found that atrial natriuretic peptide was as good and maybe was better than the Killip classification in predicting outcome. There will always be some inter-observer variability in assigning patients to the Killip classification. Furthermore we found that when the concentration of atrial natriuretic peptide doubled the relative risk of death increased by a factor 1·7.

We were not able to prove that the measurement of atrial natriuretic peptide can be used to predict congestion, because clinical evidence of congestion developed in too few patients after the first 24 hours to allow such a conclusion. If the plasma concentration of atrial natriuretic peptide is to be clinically useful in predicting congestion it must be available in minutes or hours, like an arterial gas analysis. At present a reliable analysis of atrial natriuretic peptide takes a couple of days.

We conclude that the increase in plasma atrial natriuretic peptide at admission in patients with acute myocardial infarction depends on their degree of heart failure. Furthermore, atrial natriuretic peptide measured at entry to the hospital before treatment is started is a good predictor of mortality and therefore good at identifying patients with acute myocardial infarction who are at a low and a high risk. However, it is important not to rely on a single blood test to risk-stratify patients. Like any other test plasma natriuretic peptide should be considered in conjunction with clinical information.

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Coronary venous lipid peroxide concentrations after coronary angioplasty: correlation with biochemical and electrocardiographic evidence of myocardial ischaemia

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Abstract

Background—**Raised lipid peroxide concentrations in coronary venous plasma have been reported after coronary angioplasty in humans. This may reflect increased free radical activity after myocardial ischaemia and reperfusion. If so, it may be possible to correlate lipid peroxide concentrations with the degree of myocardial ischaemia produced during angioplasty.**

Methods—**15 patients (age range 42–70; 12 men) with stable angina pectoris undergoing angioplasty of a proximal left anterior descending coronary artery stenosis were studied. Plasma lipid peroxide and lactate concentrations were measured in sequential blood samples taken from the great cardiac vein before and immediately after one to five serial 60 second balloon inflations. The maximum ST segment shift during each balloon inflation was also measured.**

Results—**Lipid peroxide concentrations in coronary venous plasma were raised from pre-angioplasty values by more than 2 SDs of the relevant measurement error after 27 out of 46 (59%) balloon inflations. Lactate concentrations were raised after 43 out of 46 (93%) balloon inflations. No significant difference was found between the peak percentage change of either lipid peroxide or lactate concentrations after any of the first three serial inflations. The maximum ST segment shift after each of the first three serial inflations was also similar. Coronary venous lactate concentrations after balloon inflation correlated positively with the maximum ST segment shift, but did not correlate with lipid peroxide concentrations.**

Conclusions—**Raised lipid peroxide concentrations in coronary venous plasma can be detected in humans after balloon angioplasty. There is no positive correlation between lipid peroxide concentrations in coronary venous plasma after angioplasty and the degree of preceding myocardial ischaemia as assessed by either ST segment shift or lactate production. These indices showed that one to three serial 60 second balloon inflations each produce a similar degree of myocardial ischaemia. The origin of the raised lipid peroxide concentrations in coronary venous plasma after angioplasty remains unknown.**

Oxygen derived free radicals are produced during reperfusion of the ischaemic myocardium.[1 2] Such free radical activity is difficult to measure directly in humans, but can result in oxidative damage to polyunsaturated membrane phospholipids with the production of relatively stable lipid peroxides. Plasma lipid peroxides are most commonly measured by catalysing their degradation to malondialdehyde, which reacts with thiobarbituric acid to form an adduct. Thus lipid peroxide concentration is normally expressed as μM of malondialdehyde and includes any free malondialdehyde that is also present in plasma. We have previously identified raised lipid peroxide concentrations in coronary venous blood after myocardial ischaemia induced by pacing.[3] During percutaneous transluminal coronary angioplasty, recurrent brief periods of myocardial ischaemia are followed by reperfusion, and this sequence might be expected to provoke free radical generation. In an initial study of patients undergoing angioplasty of the left anterior descending coronary artery, we sampled coronary venous blood two and 10 minutes after the last balloon inflation but failed to show any increase in lipid peroxide concentrations.[4] Studies in which coronary venous blood had been sampled immediately after balloon inflation(s) have reported negative[5] and positive[6 7] results. Recent animal studies have indicated that there is a positive relation between the severity of preceding myocardial ischaemia and the degree of subsequent reperfusion injury due to oxygen radicals.[8 9] If, in patients undergoing coronary angioplasty, the production of lipid peroxides is related to preceding cycles of ischaemia and reperfusion it may be possible to correlate lipid peroxide concentrations with the degree of ischaemia produced during balloon inflation.

Patients and methods

Fifteen patients (age range 42–70; 12 men) with

Table 1 Peak lipid peroxide and lactate concentrations in the great cardiac vein before and after one to three serial 60 second balloon inflations in the left anterior descending artery

	No	*Lipid peroxides (μM)* *Mean (95% CI)*	*Lactate (mM)* *Mean (95% CI)*
Before PTCA	15	3·4 (3·1 to 3·6)	1·2 (1·0 to 1·5)
1st inflation	15	4·0 (3·7 to 4·2)*	2·7 (2·4 to 2·9)*
2nd inflation	11	3·7 (3·4 to 4·0)*	2·4 (2·2 to 2·7)*
3rd inflation	10	3·9 (3·6 to 4·2)*	2·6 (2·2 to 2·9)*
After PTCA	15	3·3 (3·1 to 3·6)	1·2 (1·0 to 1·5)

PTCA, percutaneous transluminal coronary angioplasty.
*All significantly greater than values before or after PTCA (p <0·01).

stable angina pectoris undergoing angioplasty of a stenosis in the proximal left anterior descending coronary artery were studied. Three patients had had previous myocardial infarctions (one anterior, two inferior), all more than 12 months before the study. All regular medications were continued including calcium antagonists (12), β adrenoceptor antagonists (five), nitrates (nine), and 150 mg aspirin daily (15 patients). Blood samples from the great cardiac vein were taken with a 7F Gensini catheter placed through a left antecubital fossa vein. The position of the catheter was confirmed radiologically. All samples were taken after systemic heparinisation. Simultaneous aortic and coronary venous samples of 20 ml were taken before the first inflation and at the end of the procedure. Additional coronary venous samples of 10–12 ml were taken 0, 30, and 60 seconds after each inflation up to a maximum of five inflations per patient. Serial samples were taken to avoid missing the period of peak release of lactate or lipid peroxides. In the final three patients serial aortic and coronary venous blood was sampled simultaneously but only after the first inflation. All inflations were of 60 seconds duration. The protocol was appoved by the ethics committee, Glasgow Royal Infirmary and patients gave informed written consent.

ASSAYS

Lipid peroxides were measured in plasma (with added ethylenediaminetetra-acetic acid (EDTA)) by high performance liquid chromatography according to a modification of a previously described method.[4 10] Many other compounds, including some drugs, can interfere in the thiobarbituric acid assay for lipid peroxides. With high performance liquid chromatography we aimed to reduce such interference compared with older methods that use spectrophotometric or fluorimetric techniques. Mean (SD) concentration from repeated measurements in this assay was 3·8 μM (0·3) giving a coefficient of variation of 8%.[11] Lactate concentration was measured by a commercially available enzymatic assay (Boehringer Diagnostica, Mannheim) with an intra-assay coefficient of variation of 0·7%. The maximum ST segment shift in any of the 12 electrocardiographic leads recorded continuously throughout each balloon inflation was measured manually by an operator who was not aware of the results of the lactate or lipid peroxide measurements.

STATISTICS

The distribution of each variable was assessed by calculating the standardised coefficients of skewness and kurtosis. All of the data were normally distributed and so the summary statistic employed is mean and 95% confidence interval (95% CI). Repeated measures analysis of variance was used to assess the overall statistical significance of the differences between lipid peroxide and lactate concentrations, and the ST segment shift at different times. Thereafter Bonferroni corrected t tests were used. Linear regression analysis was performed to examine the relation between variables. All statistical analyses were carried out with a PC version of Statgraphics (STSC Inc, Maryland, USA).

Results

The aortocoronary lipid peroxide gradient was 0·2 (0·0 to 0·4) μ mol/l before angioplasty and −0·2 (−0·4 to 0·0) μ mol/l five minutes after the final inflation (p = 0·03). The aortocoronary lactate gradients at the same times were 0·0 (−0·2 to 0·2) μ mol/l and −0·1 (−0·3 to 0·1) μ mol/l (p = 0·86).

Lipid peroxide concentrations in the great cardiac vein

No increases above pre-angioplasty concentrations occurred in two patients. The percentage of samples in the other 13 patients with concentrations above pre-angioplasty values ranged from 25% to 100% per patient. Overall, 82 of 136 (60%) samples assayed were raised. The peak concentration was seen at zero seconds in 32% of inflations, at 30 seconds in 39%, and at 60 seconds in 29%. The peak concentration after each of the first three serial dilatations was significantly greater than both the pre and post-angioplasty samples, which were not different from each other (table 1). The peak percentage increase from pre-angioplasty values exceeded 2 SDs of the relevant measurement error (16%) after 27 out of 46 (59%) inflations (fig 1). There was no significant difference between the peak percentage change after any of the first three serial inflations (table 2).

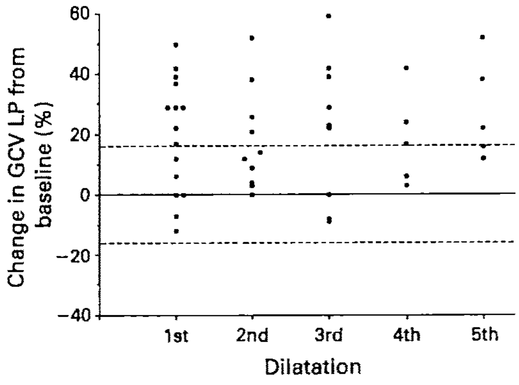

Figure 1 Individual peak percentage change in the concentration of lipid peroxide in the great cardiac vein (GCV LP) after one to five serial balloon inflations in the left anterior descending coronary artery. The broken line indicates 2 SDs of the error of repeated measurements (see text).

Table 2 Percentage change, mean (95% CI), from pre-angioplasty values of peak lipid peroxide (LP) and lactate concentrations in the great cardiac vein, and maximum ST segment shift after 1–3 serial 60 second balloon inflations in the left anterior descending artery

	No	*Lipid peroxides (%)*	*Lactate (%)*	*ST segment shift (mm)*
First inflation	15	20 (13 to 26)	147 (72 to 222)	0·8 (0·6 to 1·1)
Second inflation	11	17 (9 to 25)	141 (54 to 229)	0·9 (0·6 to 1·1)
Third inflation	10	24 (15 to 32)	167 (70 to 264)	0·9 (0·6 to 1·2)

No significant differences were found between values of any indices after first, second, or third inflations.

Lactate concentrations in the great cardiac vein

No increases above pre-angioplasty concentrations were seen in any of the samples from one patient. This patient also showed no electrical evidence of ischaemia but did have raised lipid peroxide concentrations. The percentage of samples in the other 14 patients with concentrations above pre-angioplasty values ranged from 33% to 100% per patient. Overall, 104 out of 122 (85%) of samples assayed were raised. The peak concentration was seen at zero seconds in 79%, at 30 seconds in 15%, and at 60 seconds in 6% of cases. The peak concentrations immediately after each of the first three inflations were significantly greater than both the pre and post-angioplasty samples, which were not different from each other (table 1). The peak percentage increase from pre-angioplasty values exceeded 2 SDs of the measurement error (1·4%) after 43 out of 46 (93%) inflations (fig 2). There was no significant difference in the peak percentage changes between any of the first three serial inflations (table 2).

Electrocardiographic changes

There was no significant difference in the maximum ST segment shift occurring between any of the first three serial inflations (table 2).

Correlations

A significant positive correlation was found between peak lactate concentrations in the great cardiac vein and maximum ST segment shift after each balloon inflation. No correlation was shown, however, between peak lactate and lipid peroxide concentrations in the great cardiac vein. There was a significant negative correlation between the peak concentrations of lipid peroxides in the great cardiac vein and maximum ST segment shift (fig 3).

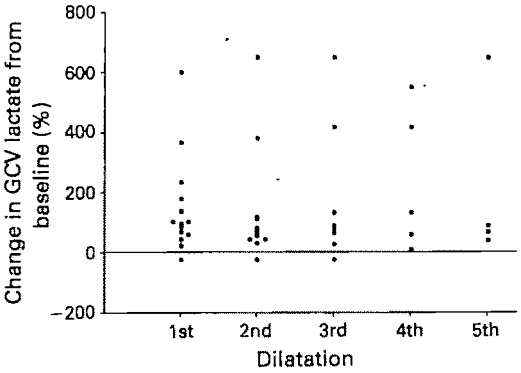

Figure 2 Individual peak percentage change in lactate concentration in the great cardiac vein (GCV) after one to five serial balloon inflations in the left anterior descending coronary artery.

Discussion

This study confirms that raised concentrations of lipid peroxides can be detected in coronary venous blood after angioplasty. It has been suggested that the production and release of lipid peroxides during coronary balloon angioplasty result from free radical mediated damage to polyunsaturated membrane lipids after cycles of myocardial ischaemia and reperfusion.[7] Our results suggest that no relation exists between lipid peroxide concentrations in coronary venous plasma after angioplasty and the degree of preceding myocardial ischaemia as assessed by either ST segment shift or lactate production. There are several possible explanations for this finding.

Firstly, we may not have produced a large enough ischaemic insult to initiate reperfusion injury. Aside from the evidence linking the degree of reperfusion injury to the extent of the preceding ischaemia as outlined in the introduction, there is some evidence that only zero flow ischaemia before reflow results in oxygen radical mediated peroxidation of membrane lipids.[12 13] We cannot determine the

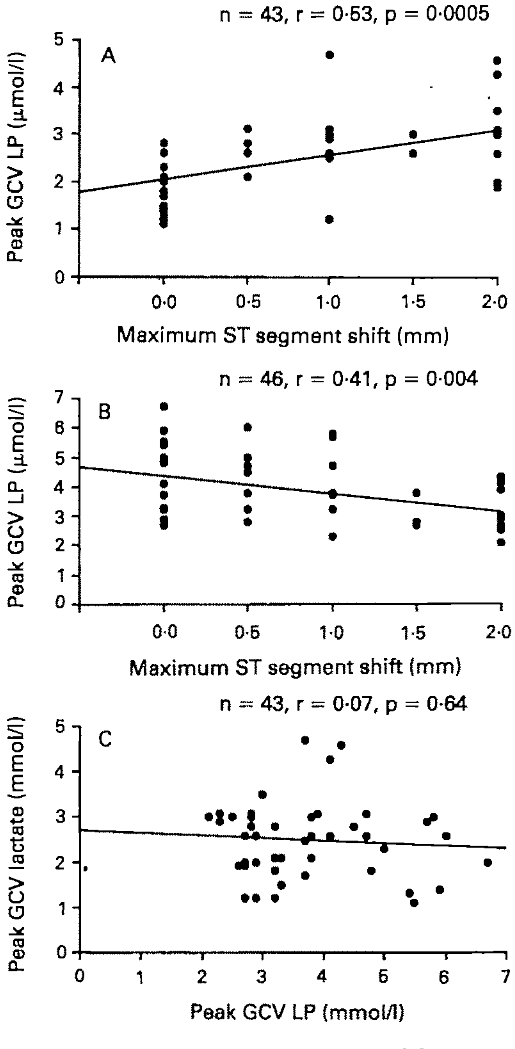

Figure 3 Simple linear regression analysis of the relation between: (A) peak lactate concentration in the great cardiac vein (GCV) and maximum ST segment shift; (B) peak GCV lipid peroxide (LP) concentration and maximum ST segment shift; (C) peak GCV LP concentration and lactate concentration.

degree of residual perfusion present during balloon inflation in our patients.

Secondly, even if severe or zero flow ischaemia were produced, we cannot be sure that the coronary venous catheter was sampling the effluent from the ischaemic area. The difficulties of assessing regional myocardial metabolism by coronary venous sampling are well known.[14 15] By sampling far into the great cardiac vein only in patients undergoing angioplasty of relatively proximal left anterior descending artery stenoses we hoped to minimise this potential problem. In 14 out of 15 cases measurements of lactate concentration confirmed that the coronary venous catheter was draining an area of at least partially ischaemic myocardium.

Thirdly, the actual sampling protocol itself may not have enabled the true trans-myocardial release of lipid peroxides to be measured. Serial samples were taken after balloon deflation, but it is possible that even frequent measurements of the concentration of a metabolite may miss the moment of peak production, particularly in the absence of any knowledge of flow. The rapid and dynamic changes in coronary artery blood flow during balloon angioplasty are such that the accurate measurement of the maximum rate of production of any metabolite would require simultaneous and continuous measurement of metabolite concentration and coronary flow.[16] This is not technically feasible at present. Baseline samples from the great cardiac vein were not taken before each inflation, but for all inflations studied, mean concentrations of both lactate and lipid peroxides were not significantly different from pre-angioplasty concentrations 60 seconds after reperfusion, a finding consistent with earlier data.[7] Ideally, one should sample simultaneously in the aorta and great cardiac vein to be certain that any changes detected in concentrations in the great cardiac vein are occurring across the coronary circulation. We did this in our final three patients and found, as did other groups, no evidence of any consistent change in the arterial concentrations of either lactate or lipid peroxides during coronary angioplasty.[5–7]

Finally, the coronary venous effluent may not reflect peroxidation of lipids within the reperfused myocardium. Studies that have measured products of lipid peroxidation in the coronary effluent and in different subcellular fractions of reperfused hearts have indicated that although there is a small rise in the lipid peroxide content of the coronary effluent after reperfusion, myocardial lipid peroxidation occurs predominantly in the membranes of certain intracellular organelles.[13 17] It is doubtful whether these lipid peroxides are free to cross the cell membrane and extracellular space and enter the circulation.

Notwithstanding these considerations the lack of any positive correlation between either the electrical or biochemical evidence of ischaemia and the raised lipid peroxide concentrations suggests that production of these can be, at best, only partly due to damage mediated by oxygen radicals after post-ischaemic reflow. Other possible sources include the mechanically disrupted atherosclerotic plaque, which is known to contain substantial amounts of lipid peroxides,[18 19] platelets,[20 21] leucocytes, and endothelial cells. These cells are all capable of producing prostaglandins, or leucotrienes, or both, and peroxides may be formed during their biosynthesis.[22 23] Even though all of our patients were taking aspirin, which interferes with the synthesis of peroxides by the cyclo-oxygenase enzyme system,[21] it is unlikely that this pathway was completely inactivated.

Irrespective of their origin, what consequences might the release of these lipid peroxides have? Lipid peroxides can selectively inhibit prostacyclin (PGI_2) synthesis[24] and through effects on antithrombin III activity[25 26] induce thrombin generation in normal plasma.[27] These prothrombotic effects could play a part in the pathogenesis of both acute occlusion and late restenosis after coronary angioplasty. Studies are needed to explore these potential mechanisms of disease and to identify the origin of the increased lipid peroxide concentrations found after angioplasty.

A secondary conclusion from the results of this study is that when 60 second balloon inflations are used, the degree of myocardial ischaemia produced during angioplasty is similar after at least three serial inflations. In animal models short earlier periods of coronary occlusion can protect against ventricular arrhythmias during a subsequent sustained ischaemic insult.[28 29] This is known as ischaemic preconditioning. The exact timing of the sequences of ischaemia and reperfusion necessary to produce preconditioning and the underlying mechanisms are not clear. Several groups have used the situation of coronary angioplasty to explore this phenomenon in humans. Our finding of an absence of preconditioning with 60 second coronary occlusions is consistent with the results of three previous studies.[30 31 32] Other workers using 90 second inflations have shown a lesser degree of ischaemia after a second inflation.[33 34]

Differences in patient selection, the method of quantifying ischaemia, and the degree of collateral flow during balloon occlusion may go a long way towards explaining these opposing results. Alternatively, it may be the case that there is a critical occlusion time needed to initiate the preconditioning mechanism, this time being greater than 60 seconds. The results of further studies specifically designed to consider these questions are awaited with interest.

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Thallium scans in syndrome X

Ann C Tweddel, W Martin, I Hutton

Abstract

***Objective*—To review thallium scans in patients with angina and normal coronary arteriograms.**

***Design*—Retrospective review of data.**

***Setting*—Regional cardiac centre in Glasgow.**

***Patients*—100 patients selected from those undergoing diagnostic angiography for typical angina who had normal arteriograms (around 10%), no other cardiovascular abnormality, and available thallium scans (performed routinely before angiography).**

***Main outcome measures*—Coronary arteriography, exercise tests, and gated thallium scans at peak exercise.**

***Results*—The exercise test was positive in 30 and negative in 70 patients. Thallium defects were found in 98 patients, but no consistent pattern and no significant correlation existed between the extent of thallium defect and positive exercise test or exercise tolerance.**

***Conclusions*—Thallium defects described in 98 of 100 patients with angina and normal coronary arteriograms suggest that microvascular angina may be commoner than is generally appreciated.**

The possibility that angina might in some cases be due to small vessel disease emerged with the advent of coronary angiography in the late 1960s. After an editorial comment on one report of such cases in 1973,[1] chest pain with normal coronary arteries has come to be known by cardiologists as syndrome X. Despite the many subsequent reports, however, differences in diagnostic criteria together with the lack of direct evidence of small vessel disease, and ignorance about the underlying pathology of this putative entity, have left many unanswered questions. Indeed the prevalence of the condition is unknown, estimates varying by one or more orders of magnitude.[2] Patients with chest pain and normal coronary arteriograms present a common diagnostic problem, but there is general agreement that in most cases the pain is non-cardiac,[3] often musculoskeletal or oesophageal in origin.[4] A small proportion remains in whom incontrovertible evidence exists for inducible myocardial ischaemia, implying coronary microvascular dysfunction.[2] This has been inferred from stress induced left ventricular dysfunction.[5 6] and pacing induced lactate production as specific but insensitive evidence of myocardial ischaemia,[7–10] and evidence by a number of different techniques of reduced coronary vascular reserve.[9 11–13] Here we report the results of thallium scans in 100 patients investigated for angina but found to have normal coronary arteriograms.

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Patients and methods

PATIENTS

A total of 328 of the 3150 diagnostic coronary arteriograms performed in the cardiology department at the Glasgow Royal Infirmary during the period 1988 to 1990 inclusive were reported as normal. We reviewed these 328 normal coronary arteriograms and selected the first 100 in whom (*a*) the arteriogram was confirmed as entirely normal, (*b*) an exercise thallium scan was available, and (*c*) there was no other cardiovascular or potentially related abnormality (including overt present or known past hypertension, diabetes, or conduction defect). To obtain 100 patients who fulfilled all three criteria in this retrospective study, the first 115 of those reported to have normal coronary arteriograms were reviewed, 10 were excluded because the arteriograms were not entirely normal, and five were excluded because the resting electrocardiogram showed left bundle branch block (LBBB). All patients had been considered before investigation to have typical stable angina of effort by at least two experienced cardiologists. Maintenance treatment was continued throughout the investigations.

EXERCISE TEST AND THALLIUM IMAGING

A symptom limited maximal upright bicycle exercise test was performed in all cases during the one to two days before angiography. An ST depression of ⩾1 mm at 0·8 s past the J point was considered diagnostically positive. An intravenous injection of 60 MBq of thallium-201 was given 15–30 s before the end of exercise. Scans were then obtained with a mobile gamma camera (General Electric) fitted with a high sensitivity parallel collimator (reperfusion scans were not routinely performed). Data were acquired in list mode (Link MAPS 2000) gated to the electrocardiogram in three standard projections: 40° and 70° left anterior oblique, and anterior. Data were reconstructed into eight frames per cardiac cycle and viewed both as static smoothed images and in cine mode. Images were reported independently by two experienced persons unaware of the angiographic findings or patient identity. Each of the three images was subdivided into five regions (fig 1), and each region was further divided into three, giving a total of 45 segments. Thallium uptake in each region

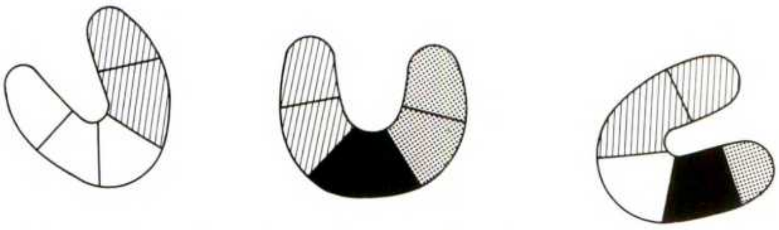

Figure 1 Anterior, 40° and 70° left anterior oblique projections, subdivided into regions. Lined area, territory of left anterior descending artery; black, right coronary artery distribution; stippled, circumflex coronary artery distribution; blank, indeterminate. Each region was further subdivided into three making a total of 45 segments.

was reported as either normal or abnormal. Figure 1 illustrates the method, showing the territories supplied by each of the major coronary vessels, with unmarked areas considered as indeterminate. The predictive accuracy of this method for detection of atheromatous coronary disease is 91% (n = 100).[14] To avoid false positive scans due to breast attenuation, septal defects in women were required to be present in all three views. The extent of the thallium defect was assessed by circumscribing the abnormality and expressing this as a percentage of the left ventricular region of interest in each projection. Wall motion was assessed by a four point scoring system (1, normal; 2, reduced; 3, greatly reduced; and 4, no motion). The reproducibility of this reporting technique is ±2% as previously reported.[14]

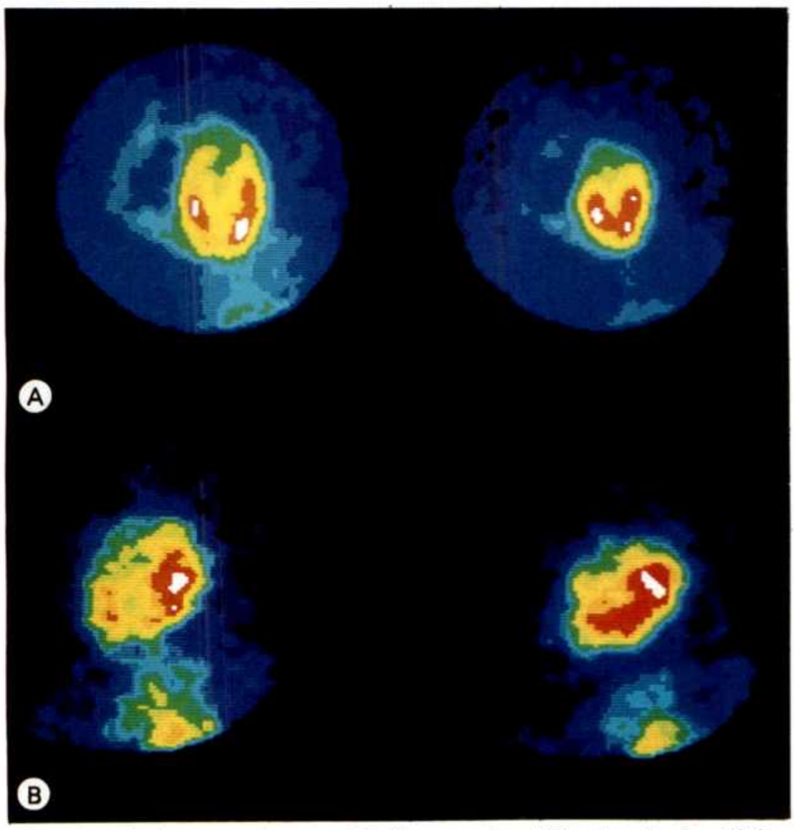

Figure 2 (A) Representative normal thallium scan, in end diastole and end systole in the 40° left anterior oblique projection, with homogeneous activity within the left ventricle. (B) Representative thallium scan showing a septal defect in end diastole and systole in the 40° left anterior oblique projection.

Results

CLINICAL AND ELECTROCARDIOGRAPHIC CHARACTERISTICS

The age range of the group was 29–64 (mean 57), and 58 of the 100 patients were women. Resting heart rate was 76 (13) (mean (SD)) beats/min and blood pressure 124 (20)/77 (10) mm Hg. None gave a history or showed electrocardiographic evidence of previous myocardial infarction. Resting electrocardiogram was normal in 61%, but showed T wave changes in 31% and ≤1 mm ST elevation in 8%. Echocardiography was not routinely performed but no patient showed evidence of left ventricular hypertrophy by electrocardiographic criteria or on left ventricular angiogram. Treatment included β blockers in 47%, calcium channel blockers in 59%, nitrovasodilators in 27%, and diuretics in 22%; 12% of patients were taking no cardioactive drugs.

The exercise test was electrocardiographically positive (≥1 mm ST depression) in 30 patients but negative in the other 70. The limiting symptom was chest pain in 44 patients, dyspnoea in 25, leg fatigue in 20, fatigue in eight, and nausea or dizziness in three.

Ninety eight patients had abnormal thallium scans. Figure 2 shows representative examples of a normal and an abnormal scan. The table shows the distribution of the defects in thallium uptake. The extent of the defect varied widely (fig 3) and showed no significant correlation with peak exercise "double product" (heart rate × systolic pressure) or with a positive exercise test though patients with positive exercise tests tended to have more extensive thallium defects (fig 4). Minor abnormalities of wall motion were seen in two patients.

Discussion

Some authors have suggested on empirical grounds that a positive exercise test be included as a necessary diagnostic criterion before patients with chest pain and normal coronary arteriograms can be diagnosed with certainty as having syndrome X, defined as angina due by implication to reduced coronary perfusion reserve at the microvascular level (microvascular angina), as distinct from the much commoner non-cardiac conditions.[2] The exercise test is nevertheless recognised as having limited specificity and sensitivity[15]: we found sensitivity to be 57% (n = 100) at a specificity of 75% for angiographically significant coronary disease (unpublished observations). Inclusion of the exercise test may thus underestimate the true prevalence of microvascular angina, which has been estimated on

Segments with defective thallium uptake

Segment	*No*	*Segment*	*No*
A	14	AI	15
Ap	2	PI	8
I	11	AP	19
P	2	PIA	27

A, anterior; Ap, apical; I, inferior; P, posterior.

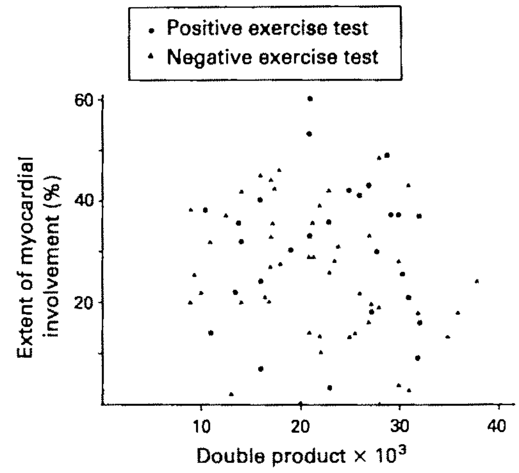

Figure 3 Extent of thallium defect expressed as % total left ventricle, plotted against the product of heart rate × systolic blood pressure on exercise (double product).

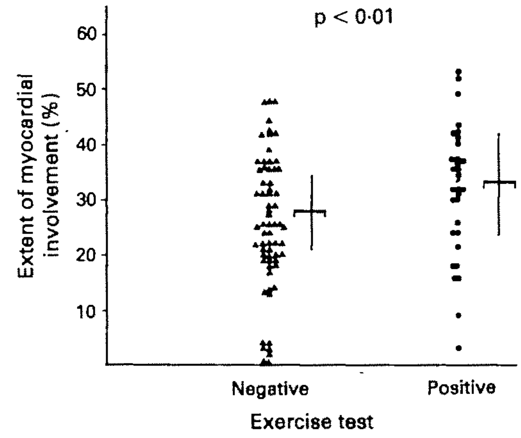

Figure 4 Extent of myocardial involvement in patients with positive and negative exercise tests. The mean is represented by the horizontal bar with the SD shown as vertical bar.

this basis as <1% of diagnostic coronary arteriograms performed.[2]

Our experience was that about 10% of diagnostic coronary arteriograms were normal. This is of the same order as the 10%–30% reported by other units.[4 16] Only 30 of our 100 patients had electrocardiographically positive exercise tests but almost all (98%) had abnormal thallium scans. This high proportion must be viewed in the context of our practice of generally using the thallium scan as a screening test before proceeding to angiography. The distribution of thallium defects was wide with no consistent pattern, and the extent of the defect was not significantly correlated with exercise tolerance or the presence of a positive exercise test.

Impairment of myocardial intracellular uptake of thallium (a potassium analogue) is due generally to impaired perfusion.[17 18] Gating images to the electrocardiogram improve their predictive accuracy to 91% in respect of significant epicardial coronary disease.[14] Thallium defects were not found in 14 volunteers whose scans were reported after interspersing them blindly among the scans of this patient population. Thallium defects are thus strongly suggestive of critically reduced perfusion. No patients in this series showed evidence of hypertrophy, heart failure, overt hypertension, LBBB, or primary cardiomyopathy, which can be associated with thallium defects[19] and none had diabetes. Artefactual defects due to breast attenuation or relative apical thinning were also excluded. Finding defects in thallium uptake on peak exercise in such a large proportion of the total number of patients undergoing diagnostic coronary arteriography suggests that inducible myocardial dysfunction, consistent with microvascular angina, may be much commoner than has been recognised from less sensitive tests.

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Use of an autoperfusion catheter in the treatment of acute refractory vessel closure after coronary balloon angioplasty: immediate and six month follow up results*

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Abstract

***Objective*—To determine the usefulness of the Stack autopersion dilatation catheter in patients with acute recurrent vessel closure during coronary angioplasty.**

***Design*—Prospective data collection.**

***Setting*—University hospital.**

***Patients*—In 37 of 1003 consecutive patients undergoing angioplasty between November 1989 and December 1990 acute vessel closure developed that could not be redilated by a conventional balloon catheter. 13 (35%) of these 37 patients were sent immediately for emergency bypass surgery.**

***Intervention*—In the remaining 24 patients an attempt was made to reopen the vessel with a Stack catheter.**

***Main outcome measure*—Successful reopening of the vessel. All successfully treated patients were followed for at least six months to detect recurrent ischaemia.**

***Results*—In 16 patients (67%) the Stack procedure was successful. Of the eight patients in whom reopening of the occluded vessel was not achieved, seven were sent for bypass surgery and one was successfully treated by emergency stent implantation. The 16 patients successfully treated with the Stack autoperfusion system were followed up for a mean (SD) of 6·7 (2·6) (range 2 to 11) months. Ten patients remained symptom free but early clinical restenosis developed in four (25%). Overall, only three (19%) of 16 patients experienced recurrence of severe (class III-IV) symptoms and required further mechanical revascularisation.**

***Conclusion*—These data support the use of the Stack autoperfusion catheter system in selected patients with acute vessel closure not responsive to attempted redilatation with conventional balloon catheters. The short-term outcome seen in this series of patients who were successfully treated with this coronary autoperfusion system is encouraging.**

Acute reocclusion remains a major problem during and after percutaneous transluminal coronary angioplasty.[1 2] It is the main cause of post-procedural emergency surgery, myocardial infarction, and even death. Acute reocclusion is generally treated with conventional redilatation. Prolonged inflations are often attempted but the development of severe anginal pain, hypotension, or electrical instability often limits the inflation time. An autoperfusion catheter can be used to permit longer inflation times.[3 4]

We report our experience with the Stack autoperfusion balloon catheter in the treatment of patients with acute vessel closure after angioplasty in whom attempted redilatation with a conventional balloon catheter was unsuccessful.

Patients and methods

In the first year after the introduction of the Stack autoperfusion balloon catheter at our centre (in November 1989) a total of 1003 coronary angioplasties were performed. On our computerised angioplasty registry[5] we identified all the patients (37) who developed persistent and acute vessel closure after attempted redilatation with a conventional balloon catheter. Thirteen of these 37 patients were sent immediately to bypass surgery because the angioplasty operator judged the underlying dissection to be so extensive and complex as to preclude success with an autoperfusion catheter system. In one of these 13 patients the left main stem was dissected by the guiding catheter, in eight there was an extensive dissection of the proximal left anterior descending artery including one or two major diagonal branches, and in the other four the occlusive dissection started proximal on a dominant right coronary artery and extended to the crux. In the remaining 24 patients we attempted to restore patency of the occluded vessel with a Stack autoperfusion balloon catheter system (Advanced Cardiovascular Systems, Temecula, California).

CLINICAL AND ANGIOGRAPHIC DEFINITIONS

Clinical data were collected from the angioplasty registry data base and the hospital records. The angina class was assigned according to the Canadian Cardiovascular Society Classification.[6] Current cigarette smokers were defined as patients who admitted to smoking any amount regularly within three months of presentation. Arterial hypertension and

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diabetes mellitus were defined as necessitating treatment. Family history of coronary artery disease was one that included parents or siblings. Lipid values were obtained after a 14 hour fast, and hypercholesterolaemia was defined as a fasting serum cholesterol concentration > 6·2 mmol/l.[7]

Coronary lesions were visually estimated in two perpendicular views and expressed as the percentage of diameter reduction as compared with the nearest "normal" arterial segments. A lesion was considered to be clinically significant when the mean value of the two views was ⩾50%. The characteristics of individual lesions were entered into the data bank and we used the modified American Heart Association/ American College of Cardiology scoring system to classify the lesions.[7] Primary clinical success was defined as a ⩾20% reduction in luminal narrowing to a residual narrowing of <50% without the occurrence of death, myocardial infarction, or emergency surgery. Myocardial infarction was defined as an increase in cardiac enzymes (to more than twice the upper normal limits of creatine kinase and for an MB fraction >4%).

TECHNIQUE

All percutaneous transluminal coronary angioplasty procedures were performed via the femoral or brachial approach with a rail-type device as detailed previously.[2] All images were recorded by a high definition digital Polytron system (Siemens, Erlangen, Germany) that allows real time acquisition on and immediate postprocessing recall of the acquired images.

Premedication routinely consisted of aspirin 100 mg daily, calcium antagonists, and an heparin infusion a rate of 1000 IU/h. At the start of the procedure an intra-arterial bolus of heparin (10 000 IU) was given and a bolus of 5000 IU was repeated if the procedure lasted more than an hour. After the procedure the heparin infusion was continued for 24 hours and treatment with calcium antagonists and aspirin for six months. If we could not obtain a sustained satisfactory result with the conventional balloon we introduced the Stack catheter on an extension wire. The wire was then withdrawn and positioned proximal to the sideholes of the balloon catheter in order to allow continuous perfusion during balloon inflation. After balloon inflation, the guiding catheter was pulled back carefully over a few centimetres to ensure free flow through all its sideholes. Before we removed the Stack catheter we repositioned the guiding catheter and advanced the wire into its original distal position before the final angiograms were obtained.

PATIENT FOLLOW UP

After hospital discharge repeat coronary angiography was only performed if it was judged to be clinically indicated. Every patient was scheduled for an outpatient visit and functional testing at least six months after angioplasty. Follow up data were obtained from clinical records and physician mail or telephone questionnaire.

STATISTICAL ANALYSIS

Data are expressed as mean (SD). We used the unpaired t test for intergroup comparison. A p value of ⩽0·05 was regarded as significant.

Results

BASELINE CHARACTERISTICS

Table 1 shows the baseline clinical characteristics of the 24 study patients. All patients underwent single lesion angioplasty. In 13 patients the attempted lesion was located in the left anterior descending artery, in seven patients it was in the right coronary artery, and in the remaining four patients it was in the left circumflex artery. A type A lesion was dilated in four patients whereas types B1 and B2 lesions were present in 10 patients each. Despite repeated attempts at redilatation with a conventional balloon catheter (mean cumulative inflation time of 418 s (range 100–1500)) sustained vessel patency could not be achieved in any of these 24 patients. In 11 patients (46%) recurrent thrombus formation was the most striking angiographic finding, whereas in 13 patients (54%) a double lumen contour caused by dissection was most prominent. All 24 patients had both persisting ischaemic electrocardiographic changes and severe chest pain during and after these conventional balloon inflations.

SHORT TERM OUTCOME

The mean balloon size of the Stack catheter resembled that of the previously used balloon (2·92 (0·24) mm *v* 2·77 (0·66) mm; p = NS)) and the Stack balloon inflation time was 1728 (1316) s. In only three patients were both the clinical and electrocardiographic signs of ischaemia suppressed during the Stack balloon inflation. In three other patients only the ischaemic electrocardiographic changes disappeared and one patient became free of chest pain despite the persistence of electrocardiographic changes. In the remaining 17 patients (71%) minor electrocardiographic changes persisted during Stack inflation while the intensity of the chest pain was sufficiently reduced to allow inflation times of many minutes. In 16 patients (67%) a rewarding angiographic result was achieved (percentage

Table 1 Baseline characteristics of 24 patients treated with an autoperfusion catheter

Variable	*Result*
Female/male ratio	5/19
Age (yrs) (mean (SD))	57·4 (9·3)
Cholesterol (mmol/l) (mean (SD))	6·28 (1·12)
Smoking (n):	
Never	5
Ex	10
Current	9
Systemic hypertension (n)	8
Diabetes mellitus (n)	5
Previous myocardial infarction (n)	12
Angina class I-II* (n)	6
Angina class III-IV* (n)	18
Vessel disease (n):	
1	15
2	8
3	1
Ejection fraction (%) (mean (SD))	69·6 (10·9)

*Canadian Cardiovascular Society classification.

Table 2 Angiographic characteristics of the lesions successfully and unsuccessfully dilated by the Stack autoperfusion balloon catheter

Characteristic	*Successful (n = 16)*	*Unsuccessful (n = 8)*
Arteries (n):		
RCA	5	3
LAD	2	4
LCX	9	1
Subtotal and total occlusion (n)	5	1
Long stenotic segment (n)	3	2
Multiple stenoses* (n)	1	0
Located in a bend >45° (n)	3	3
Eccentric (n)	8	6
Calcified (n)	3	4
Presence of thrombus (n)	4	3
Lesion classification† (n):		
A	3	1
B1	7	3
B2	6	4
Stenosis diameter (%) (mean (SD))	91 (3)	91 (3)

*Multiple stenoses within the same balloon length; †modified ACC/AHA classification system; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery. No statistically significant differences were found between the groups.

diameter obstruction before 91 (6)% *v* 19 (10)% after dilatation) and in only three of these patients was a non-obstructive intimal flap visible on the final angiograms. In three of these patients there was a slight increase in creatine kinase (<200 IU/l, normal range 10–70 IU/l) within 24 hours. This finding was considered to be related to the occlusion of a minor side branch in one patient and to prolonged episodes of severe ischaemia during a complicated dilatation procedure in the two others. In eight (33%) patients the Stack dilatation was unsuccessful. Emergency bypass surgery was performed in seven but the most recent failure was successfully treated with a balloon expandable stent. Table 2 gives detailed descriptions of the lesions both subgroups (successful and unsuccessful Stack dilatation).

FOLLOW UP RESULTS

The 16 patients successfully treated with the Stack autoperfusion catheter were followed up for 6·7 (2·6) (range 2–11) months. Ten patients remained totally symptom free but severe (class III-IV) and mild (class I–II) anginal symptoms recurred in three patients each. Repeat coronary angiography showed restenosis in four patients and progression of disease in an undilated vessel and insignificant findings in one patient each. Two of the three patients with severe symptoms had elective surgery and in one patient repeat coronary angioplasty was performed. The three patients with minor symptoms were all treated medically.

Discussion

We found that an autoperfusion balloon catheter could be used to treat acute vessel closure after coronary angioplasty when attempted redilatation with the conventional balloon had been unsuccessful. All 16 (43% of 37) patients in whom autoperfusion was successful would otherwise have been candidates for emergency bypass surgery. The restenosis rate after successful autoperfusion was similar to that after conventional angioplasty.

An autoperfusion catheter was first used in 1988 to perform very prolonged balloon inflations during clinical angioplasty. Stack's group used the catheter in 11 patients undergoing elective angioplasty and showed that if significantly reduced ischaemic symptoms and signs during angioplasty, thus allowing prolonged periods of balloon inflation.[3 4] Use of the Stack coronary autoperfusion catheter was later extended to the treatment of acute vessel closure caused by large dissections during angioplasty.[8 9] The appealing rationale for the use of the autoperfusion catheter in this setting was that the prolonged balloon inflations allowed by this catheter could be effective in "tacking up" the intimal flap.[9]

There are only a few reports, mainly preliminary studies, about the use of this catheter system in the treatment of acute vessel closure. Saenz *et al*[8] reported excellent results in 22 patients with acute occlusion or obstructive dissection during angioplasty (in 20 of them an attempt to correct the angiographic appearances with a conventional balloon had failed). A successful result was achieved with the autoperfusion catheter in all but one patient: this patient underwent coronary bypass surgery 48 hours after the procedure. Leitschuh *et al* reported use of the Stack autoperfusion catheter in 22 patients with coronary dissection at angioplasty.[10] Angiographic success was achieved in 19 (86%): one patient (5%) died and one patient required emergency bypass surgery. Hodes *et al* used the Stack catheter in two clinical settings during angioplasty.[9] In 17 patients the indication for use of this catheter was treatment of dissection with repeated total or subtotal reocclusion. In four patients, all with compromised left ventricular function, the indication was the prevention of profound ischaemia during angioplasty. Success was achieved in 15 (71%) of these 21 patients: one patient died and three required emergency coronary bypass surgery. In contrast to our study, none of the earlier, mainly preliminary, studies reported in what proportion of all their patients with acute vessel closure, not responsive to redilatation with a conventional balloon, use of a coronary autoperfusion catheter was attempted. In our series we attempted to treat refractory acute vessel closure with a Stack catheter in two thirds of the patients with this complication. In the other third, the angioplasty operator judged that the underlying dissection was too extensive for use of the autoperfusion catheter to be successful. The successful deployment of an intracoronary stent in one of the eight patients in whom we failed to achieve a successful angiographic result with the Stack catheter illustrates yet another approach to avoiding surgery in patients with acute vessel closure.

Also in contrast to our study none of the earlier studies reported follow up results after successful use of a coronary autoperfusion catheter in patients with acute vessel closure. In our study, at short-term follow up most of the patients were angina free or had only mild symptoms. In particular, the clinical restenosis rate (25%) in our series resembles that reported after conventional balloon dilatation.[2] The latter observation is of interest because several clinical studies have suggested that use of long inflations might reduce the restenosis rate after angioplasty.[11] However, Quigley *et al* have recently reported the short-term follow up in 63 patients undergoing elective angioplasty with long inflations and the Stack autoperfusion catheter.[12] Angiographic restenosis developed in 19 (30%) of these 63 patients. This observation led Quigley *et al* to conclude that use of prolonged inflations did not reduce the restenosis rate.[12]

As with the other reports of the use of a coronary autoperfusion system in the treatment of acute vessel closure, the present study is somewhat limited by the number of patients and the retrospective nature of the study. However, our experiences were encouraging. Finally, since our centre and others are now evaluating the usefulness of newly developed balloon expandable stents as an alternative treatment for this complication, the present data may serve as reference and base for comparison.

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CASE REPORTS

Regression of left ventricular hypertrophy in a transplanted heart

S C D Grant, A N Rahman, N H Brooks

Abstract

A woman with advanced coronary artery disease underwent heart transplantation. The donor heart had left ventricular hypertrophy. The electrocardiographic and echocardiographic evidence of left ventricular hypertrophy regressed during follow up; estimated left ventricular mass decreased from 393 g to 171 g. The adaptation of myocardial mass and performance after transplantation is not fully understood. This case illustrates the potential for regression of left ventricular hypertrophy in response to altered loading conditions.

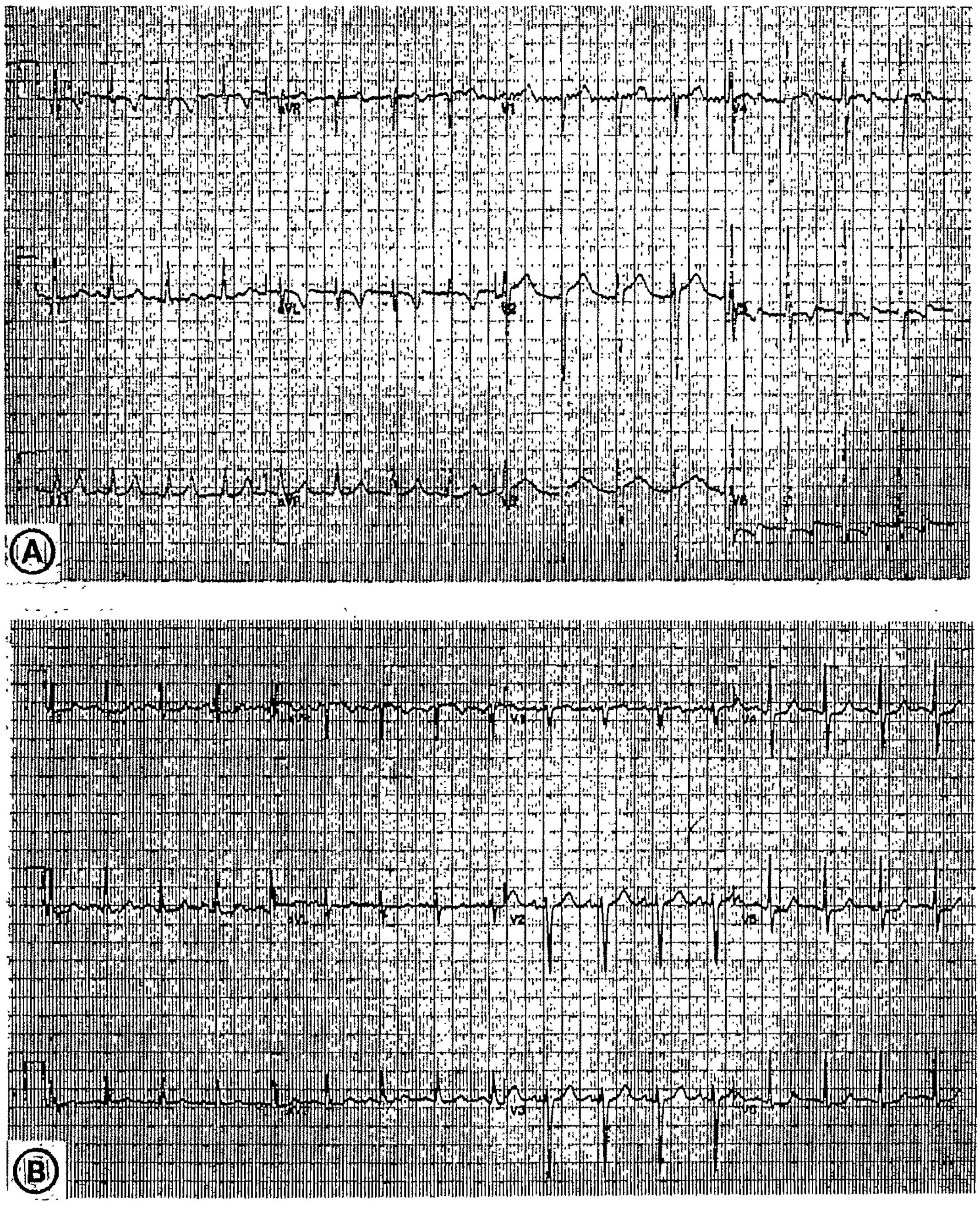

Figure 1 12 lead electrocardiograms: (A) Immediately after transplantation, (B) 25 months after transplantation. Comparison shows a reduction in left ventricular hypertrophy.

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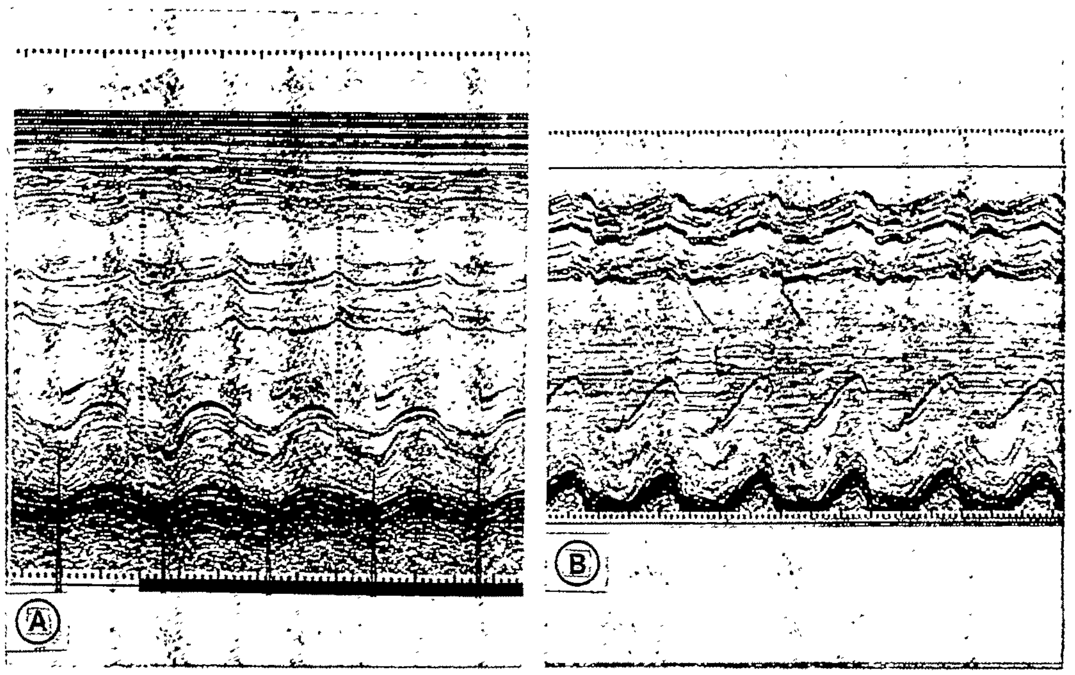

Figure 2 M Mode echocardiograms at the level of the left ventricle: (A) Immediately after transplantation, (B) 25 months after transplantation. Comparison shows a considerable reduction in left ventricular posterior wall and septal thickness.

The human myocardium responds to changes in demand upon it by changes in myocardial mass. The capacity of the transplanted heart to respond in this way is not well documented. A case is described in which the features of left ventricular hypertrophy in a donor heart regressed within a few months of transplantation.

Case report

A 53 year old woman with advanced heart failure secondary to coronary artery disease underwent orthotopic cardiac transplantation in November 1988. She received the heart of a 29 year old man of 71 kg who had died of a subarachnoid haemorrhage. He had had no medical history. His chest *x* ray was normal. When the organ was harvested it was noted to be bulky with left ventricular hypertrophy but no evidence of aortic stenosis. It was assumed by the donor team that the changes must have been due to previous hypertension, although his blood pressure recorded on the intensive care unit had been normal.

Standard orthotopic transplantation was carried out without complications and subsequent progress of the recipient has been uneventful; she remains well two and a half years after transplantation. She has had a single episode of moderate rejection on biopsy (grade 3a), which quickly resolved with a short period of augmented oral steroids. Her immunosuppressive regime is; 125 mg of cyclosporin twice daily and 5 mg of prednisolone and 150 mg of azathioprine once daily. She takes 10 mg of nifedipine and 40 mg of sotalol twice daily for cyclosporin induced hypertension and recurrent atrial tachyarrhythmias.

Electrocardiogram and echocardiogram immediately after the transplantation (figs 1 and 2) showed left ventricular hypertrophy with a left ventricular mass of 393 g (estimated from the cube rule[1]). Over several months these changes resolved with the electrocardiogram being normal at nine months. Her most recent electrocardiogram and echocardiogram are also shown in figs 1 and 2. The current estimate of left ventricular mass is 171 g.

Discussion

Normal myocardium responds to changes in demands upon it by changes in mass. Hypertrophy can occur quickly in experimental animals one to six weeks[2,3] and this has also been shown in studies on the response of human myocardium to training[4] and pregnancy,[5] when again echocardiographic measurements of left ventricular mass show an increase within a period of weeks.

In transplantation it is unlikely for recipients to receive a donor heart that is exactly matched to their needs and therefore some degree of hypertrophy or involution might be expected. Little work has been done to show that this does in fact occur. Angermann *et al* have shown that the transplanted myocardium can both hypertrophy and regress in response to recipient hypertension and it's treatment.[6] Hosenpud *et al* compared donor:recipient weight ratio at three months after transplantation and found that although normal cardiac output is maintained in proportion to recipient weight, in patients who have received a heart from a lighter donor this is achieved at the expense of a higher heart rate and resting pulmonary capillary wedge pressure.[7] This suggests that the myocardium has either failed to adapt, or has done so only partially by three months after transplantation. It has been suggested that this relation does not persist at 12 months,[8] which would be in keeping with the idea of gradual adaptation of the donor heart to its new loading conditions over a period of three to 12 months. A recent report retrospectively assessed the effect of donor:recipient weight mismatch on outcome and suggested that, contrary to popular belief, oversizing (that is a donor weight in excess of recipient ideal weight) results in a poorer outcome.[8] There was a continuous (negative) relation between degree of oversizing and survival. It was also concluded that undersizing was not detrimental to allograft function and survival.

Further work on the correlation between size match and ultimate outcome is required to define the optimal limits of size matching.

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Giant right atrial diverticulum: an unusual cause of Wolff-Parkinson-White syndrome

K Shah, K Walsh

Abstract

A case of a giant right atrial diverticulum associated with neonatal supraventricular tachycardia is reported. The electrocardiogram in sinus rhythm showed pre-excitation that may have been caused by the right atrial diverticulum adhering to the right ventricle.

Congenital diverticulum or aneurysm of the right atrium is a very rare anomaly. Morrow *et al* reported the case of a 23 year old woman with a large congenital aneurysm of the right atrium that caused repeated attacks of supraventricular tachycardia and was successfully treated by surgical resection of the diverticulum.[1] A case of atrial tachycardia in a five month old infant caused by multiple congenital saccular aneurysms of the right and left atrium that was successfully treated surgically has also been reported.[2] Aneurysms of the left atrium have also been reported to be associated with atrial arrhythmias.[3] Our case was noticed prenatally, was subsequently diagnosed with cross sectional echocardiography, and was successfully treated with antiarrhythmic drugs.

Case report

A 29 year old woman (para 1, gravida 3) was referred at 35 weeks' gestation after a four chamber view of the fetal heart could not be obtained. Ultrasound examination of the heart showed an unusually dilated right atrium and right ventricle with normal attachment of the septal tricuspid valve leaflet. No other cardiac abnormality was found to explain the right atrial and ventricular enlargement.

Karyotyping of a sample of fetal cord blood showed normal chromosomes. In view of cardiac abnormality detected, delivery was induced at 38 weeks' gestation at the regional neonatal unit. A male baby weighing 3 kg was delivered normally and was in good condition at birth. Within two hours of birth he developed supraventricular tachycardia at a rate of 275 beats per minute. He was treated with oral digoxin and intravenous flecainide and the heart rate slowed to 225 beats per minute (fig 1A). The following day because the arrhythmia had persisted he was given 5 J and then 10 J of direct current synchronised cardioversion without effect. The next day he converted to sinus rhythm with a short PR interval and a delta wave with a pattern typical of type B Wolff-Parkinson-White syndrome (fig 1B).

Echocardiography, performed when supraventricular tachycardia first developed, showed a large diverticulum (fig 2) arising from the lateral right atrial wall and extending over the right ventricle to its apex. The wall of the diverticulum seemed to be trabeculated internally and to contract during the tachycardia. Strands of muscle tissue crossed the diverticulum. The right ventricular free wall was concave and it looked as if the right ventricle was being compressed by the diverticulum. However, the tricuspid valve measurements were within normal limits and there was no disturbance of Doppler flow patterns within the right ventricle. Contrast echocardiography performed through a peripheral venous line showed microbubbles entering the diverticulum where they seemed to persist and whirl about. A chest *x* ray showed a very prominent right atrial shadow. He was discharged home on flecainide and digoxin. During follow up for one year he thrived and had no recurrence of supraventricular tachycardia. His electrocardiogram continues to show type B Wolff-Parkinson-White syndrome. Repeated echocardiography and ventilation/perfusion scans showed no evidence of thrombus formation within the diverticulum or embolism to the lungs.

Discussion

Neonatal supraventricular tachycardia is generally associated with a structurally normal heart and is usually caused by an accessory pathway. When neonatal supraventricular tachycardia is associated with congenital heart disease the most likely diagnosis is Ebstein's anomaly, which can be associated with type B Wolff-Parkinson-White syndrome. In our patient enlargement of the right atrium caused by a diverticulum was congenital. There was no evidence that this diverticulum was secondary to tricuspid valve regurgitation. On echocardiography the aneurysm seemed to arise from the free wall of the right atrium and extended across the front of the heart to reach the left ventricular apex. No distinct right atrial appendage was seen. The wall of the diverticulum seemed to be muscular and contracted with atrial systole. The patient of Morrow and Behrendt had a structurally similar aneurysm in terms of origin and disposition on the cardiac surface. Histology of the resected aneurysm in their patient showed that the wall of the

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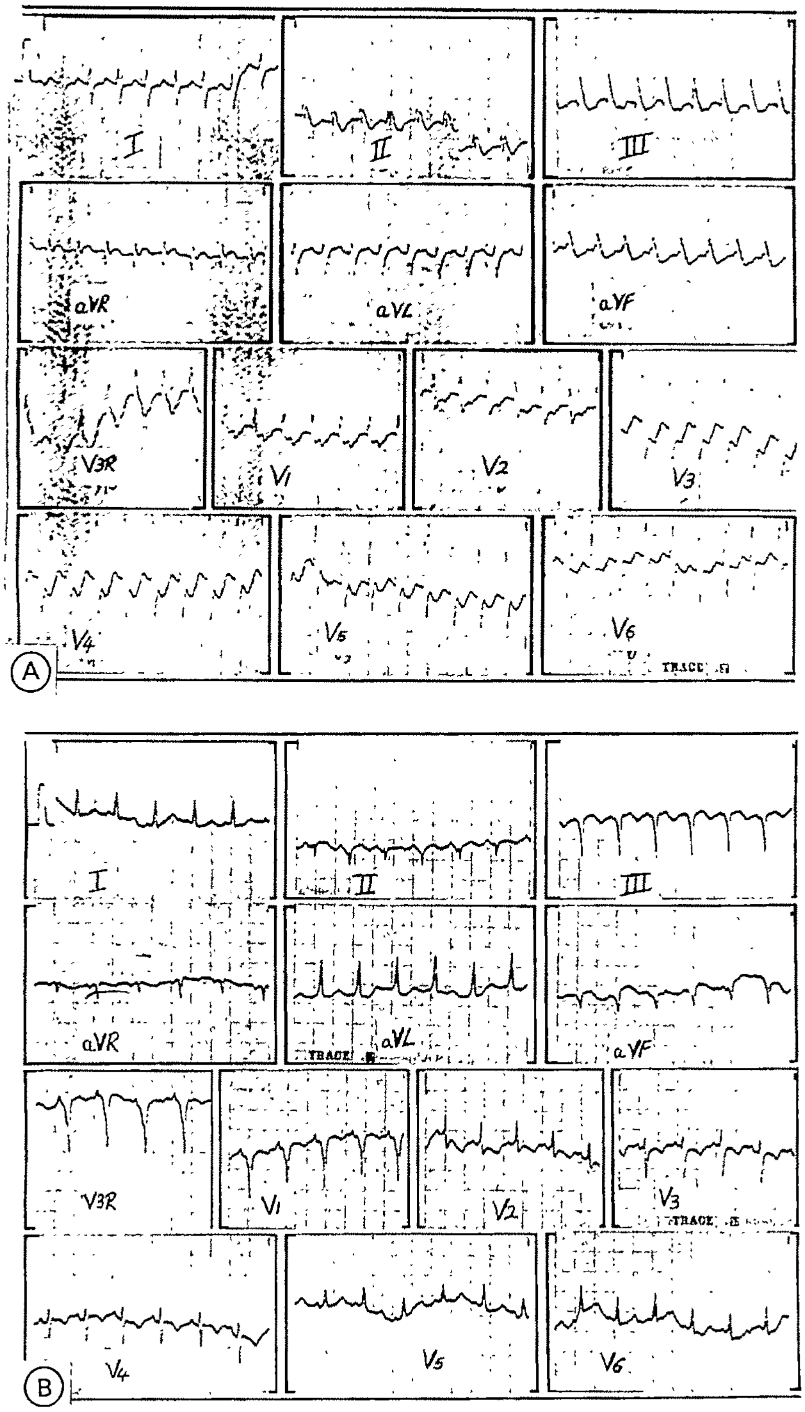

Figure 1 (A) Electrocardiogram showing narrow QRS complex tachycardia at a rate of 225 /min, with P wave visible in the ST segment suggesting atrioventricular reentry. (B) Electrocardiogram in sinus rhythm showing a short PR interval and delta wave, characteristic of type B Wolff-Parkinson-White syndrome.

diverticulum was composed of fibrous tissue and attenuated muscle fibres with an endothelial lining. The atrial diverticulum in their patient case was easily reflected off the ventricules suggesting that there was an intervening serous space lined by visceral pericardium. The echocardiogram in our patient showed that the diverticulum was directly adherent to the anterior surface of the right ventricle and left ventricle and that there seemed to be large muscle bundles arising from the ventricular aspect of the diverticulum that protruded into the cavity of the diverticulum. The right ventricle in our patient and that of Morrow and Behrendt seemed to be compressed by the diverticulum. However, in our patient Doppler study did not show any restriction of tricuspid valve inflow or right ventricular outflow.

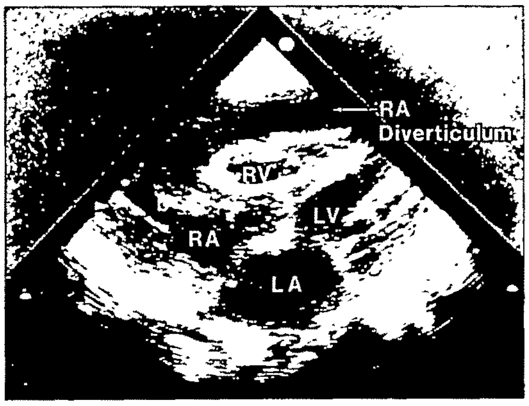

Figure 2 Subcostal four chamber cross-sectional echocardiogram showing right atrial diverticulum in front of the compressed right ventricle (arrow). RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

Most of the patients reported with aneurysms or diverticula of the left or right atria have had episodes of supraventricular tachycardia that have been stopped by excision of the aneurysms. The mechanism of the supraventricular tachycardia in these patients had been ascribed to either atrial ectopic tachycardia or atrial re-entry tachycardia. In contrast, our patient seemed to have ventricular pre-excitation, caused by the direct contact between the aneurysm and the ventricular surfaces. Ventricular pre-excitation has also been reported in patients with aneurysms of the coronary sinus or veins. The muscle bundles have been shown to run in the walls of these vessels and cross from atrium to ventricle, thus providing a pathway for ventricular pre-excitation.[4 5]

This patient's arrhythmia was fairly easily controlled with digoxin and flecainide. However, it is likely that he will require surgical excision in the future to reduce the risk of thrombus formation and possibly to eliminate the ventricular pre-excitation that could result in rapid anterograde conduction during atrial fibrillation[6]; this would be more likely to occur with a large atrial cavity.

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EPIDEMIOLOGY

Plasma triglyceride and high density lipoprotein cholesterol as predictors of ischaemic heart disease in British men

The Caerphilly and Speedwell Collaborative Heart Disease Studies

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Abstract

***Objective*—To assess the roles of plasma triglyceride and high density lipoprotein (HDL) cholesterol concentrations in predicting ischaemic heart disease.**

***Design*—Two prospective cohort studies with common core protocols.**

***Setting and participants*—Both cohorts are 100% samples of middle aged men. In Caerphilly the 2512 men were living within a defined area. In Speedwell the 2348 men were registered with local general practitioners.**

***Main outcome measures*—Fasting blood samples were taken at initial examination and plasma lipid concentrations were measured. Major ischaemic heart disease events were assessed from hospital notes, death certificates, and electrocardiograms.**

***Results*—At first follow up, after an average of 5·1 years in Caerphilly and 3·2 years in Speedwell, 251 major ischaemic heart disease events had occurred. Men with triglyceride concentrations in the top 20% of the distribution had a relative odds value for ischaemic heart disease of 2·3 (95% confidence interval (95% CI) 1·3 to 4·1) compared with men in the bottom 20%, after adjusting for both plasma total and HDL cholesterol, and non-lipid risk factors. Men in the lowest 20% of the distribution of HDL cholesterol concentration had a relative odds value of 1·7 (95% CI 1·0 to 2·8) compared with the top 20%, after adjustment was made for total cholesterol and triglyceride concentrations, and non-lipid risk factors. These relations were not caused by β blockers, which were being taken by 5% of the men.**

***Conclusions*—Plasma triglyceride concentration predicts major ischaemic events after allowance is made for total and HDL cholesterol concentrations and other risk factors. In these populations, triglyceride is a more important predictor than total cholesterol concentration.**

Many studies have shown that total cholesterol concentration is an important predictor of the development of ischaemic heart disease.[1-3] Interest in the role of high density lipoprotein (HDL) cholesterol in the aetiology of ischaemic heart disease was stimulated in 1975 by Miller and Miller.[4] Since then, numerous epidemiological studies have shown that low concentrations of HDL cholesterol are independently associated with an increased risk of ischaemic heart disease.[5] The first British study, however, to report on this association concluded that HDL cholesterol was not a major risk factor.[6] A later report, based on a larger number of events and with a different method of analysis, revised that view and concluded that HDL cholesterol was important, but less so than total cholesterol concentration.[7]

Raised concentrations of total triglyceride are associated with an increased risk of ischaemic heart disease. Most studies suggest that, in men, triglyceride is not an independent risk factor and that its relation with ischaemic heart disease is explained by the association of both with other factors, particularly total cholesterol and HDL cholesterol.[7 8] This, however, has not been a universal finding and the role of triglyceride is still uncertain.[9] Understanding of this role is complicated by the fact that in some studies triglycerides were measured after the subjects had fasted overnight, whereas in others the subjects had not.

The Caerphilly and Speedwell studies recruited their joint population of 4860 middle age men between 1979 and 1983.[10] Lipids were measured on fasting blood samples. In this report, the relations of triglyceride, HDL cholesterol, and total cholesterol concentration to the incidence of ischaemic heart disease are described.

Methods

STUDY POPULATIONS

In Caerphilly, a 100% sample of men was selected from within a defined area. They were aged between 45 and 59 when first examined. A total of 2512 men were seen—89% of the 2818 found to be eligible. In Speedwell, a 100% sample of men was selected from the age sex registers of 16 general practitioners working from two neighbouring health centres. The men were aged 45 to 59 when chosen, immediately before the study began. They were aged between 45 and 63 when first examined. A total of 2348 men were seen—92% of those eligible. The combined cohort thus numbers 4860 men.

SURVEY METHODS AND FOLLOW UP PROCEDURE

The two studies had a common core protocol and common procedures as described elsewhere.[10-12] Briefly, when recruited, the men attended an afternoon or evening clinic at which a standard medical and smoking history was obtained; subjects answered the London School of Hygiene and Tropical Medicine chest pain questionnaire; height, weight, and blood pressure were measured; and a 12 lead electrocardiogram was recorded. The men returned, after an overnight fast, to an early morning clinic where a blood sample was taken with minimal venous stasis and anticoagulated with 1 mg/ml disodium ethylenediaminetetraacetate. Fasting samples were obtained from 4641 men. The minimal duration of the overnight fast was eight hours and the typical duration was 12 hours.

The results reported in this paper refer to the first follow up. In Caerphilly, this was at a nearly constant interval of (mean (SD)) 61 (5) months, whereas in Speedwell the mean follow up period was 38 (3) months. At follow up the chest pain questionnaire was answered again, and a second electrocardiogram recorded. The chest pain questionnaire was extended to include questions about stays in hospital for severe chest pain. The questionnaires, together with hosptal activity analysis notifications of admissions coded as 410–414 (ischaemic heart disease) on the International Classification of Diseases (ICD), were used as the basis for a search of hospital notes for events which satisfied the World Health Organisation (WHO) criteria for definite acute myocardial infarction. For men who had died before the follow up, a copy of the death certificates was automatically received from the National Health Service Central Registry. From this information, three categories of events associated with ischaemic heart diseases were defined[12]: death from ischaemic heart disease (cause of death coded as ICD 410–414), clinical non-fatal myocardial infarction (an event satisfying the WHO criteria), and electrocardiographic myocardial infarction (appearance of major or moderate Q or QS waves, Minnesota codes 1-1-1 to 1-2-5 or 1-2-7 on the follow up electrocardiogram; when there were no Q or QS waves, Minnesota codes 1-1-any, 1-2-any, or 1-3-any on the recruitment electrocardiogram). All electrocardiograms were read by one of two highly experienced persons. The same persons read, independently, recruitment and follow up electrocardiograms for both studies.

LABORATORY METHODS

Because of the heavy workload separate laboratories had to be used for the lipid analyses for the two areas. Plasma samples were transported at 4°C by rail to the laboratories on the day of venepuncture. Cholesterol and triglyceride concentrations were measured with enzymatic procedures.[13-14] The HDL fraction was isolated by precipitation of the low and very low density lipoproteins with sodium phosphotungstate and magnesium chloride (Caerphilly),[15] or with heparin and manganese chloride (Speedwell).[16]

In both studies at least one in every 20 of the blood samples was sent to the laboratory as a split duplicate to assess reproducibility. This was similar in the two laboratories. Coefficients of variation were 7% (Caerphilly) and 10% (Speedwell) for total cholesterol, 14% and 15% for triglyceride, and 20% in both laboratories for HDL cholesterol.

Over the course of the recruitment phase, 91 of the Speedwell blood samples were split, one aliquot going to the Speedwell laboratory and the other to the Caerphilly laboratory. Mean differences in concentration between laboratories were 0·50 mmol/l for cholesterol, 0·01 mmol/l for HDL cholesterol, and 0·11 mmol/l for triglyceride. The Speedwell laboratory measured higher for cholesterol and HDL cholesterol and lower for triglyceride. These between laboratory differences were consistent from sample to sample and the variation between laboratories was indistinguishable from the variation when two aliquots were sent to the same laboratory. In all analyses the concentration of cholesterol, HDL cholesterol, and triglyceride were adjusted to that of the Speedwell laboratory using the mean differences cited.

STATISTICAL METHODS

Adjusted mean differences in lipids between various groups (tables 1, 2 and 5) were obtained by analysis of covariance with standard multiple linear regression techniques.

The rest of the analysis was performed by multiple logistic regression with the occurrence or not of a major ischaemic heart disease event as the dependent variable. Logistic regression takes no account of the duration of follow up. This is likely to be immaterial, however, as the duration of follow up was virtually constant within each area. Any model involving time would also face the problem that no time of event is available for electrocardiographically defined myocardial infarction. In the logistic regression analyses lipid concentrations were treated in two ways. Firstly, their distributions were divided into equal fifths, and the results presented as the odds of major ischaemic heart

Table 1 Mean (SD) concentrations (mmol/l) of lipids and incidence of ischaemic heart disease (IHD): areas combined*

Lipid	*No major incident IHD (n = 4408)*	*Major incident IHD (n = 233)*	*Age and area standardised mean difference (95% CI)*
Cholesterol	6·04 (1·17)	6·32 (1·38)	0·29 (0·13 to 0·44)
HDL cholesterol	1·12 (0·35)	1·04 (0·33)	−0·09 (−0·14 to −0 04)
Triglyceride	1·72 (1·16)	2·01 (1·12)	0·31 (0·16 to 0·46)

*Mean concentrations are area standardised. HDL, high density lipoprotein.

disease in each fifth relative to baseline fifth; 95% confidence intervals (95% CIs) for these relative odds were also estimated. The fifths were calculated within area, using each area's own quintiles. Secondly, the lipids were entered as continuous variables and the results presented as standardised relative odds, defined as the proportionate change in odds for a 1 SD change in the variable. Except for the essentially univariate analyses of tables 1 and 2, triglyceride concentration was transformed to natural logarithms.

Ischaemic heart disease at recruitment was assessed by the London School of Hygiene and Tropical Medicine chest pain questionnaire and the 12 lead electrocardiogram. Three categories of pre-existent disease—namely, angina, prolonged severe chest pain, and electrocardiographic ischaemia—were defined in a standard manner.[17] Among the total cohort of 4860 men, 1171 (24%) had some evidence of ischaemic heart disease. Four hundred and ninety one (10%) had asymptomatic electrocardiographic ischaemia, and 261 (5%) had had at least one episode of severe chest pain lasting more than half an hour for which they had consulted a doctor who diagnosed ischaemia or, in a small number of cases, passed no opinion to the subject.[18] This overall prevalence of ischaemic heart disease at recruitment of 24% is close to that found by the British Regional Heart Study.[3]

The men with evidence of ischaemic heart disease when first examined have not been excluded from the analysis. Reasons for this are given elsewhere.[12] Briefly, exclusion of such a large group, among whom roughly half the major events occur, does not seem satisfactory. The usual practice is to exclude a small group of subjects such as the 261 (5%) who had had an episode of prolonged severe chest pain that was considered by a doctor to be ischaemic in origin.[3] It is then assumed, incorrectly, that the remaining subjects are free of disease. Instead we have chosen (as did the Regional Heart Study) to include all men but to adjust for the presence of pre-existent disease by including standardised measures of angina, severe chest pain, and electrocardiographic ischaemia on entry to the study as three covariates in the logistic regression analyses. This is a conservative procedure that may underestimate the association between lipid concentrations and incidence of ischaemic heart disease. Deaths attributed to causes other than ischaemic heart disease were treated as events not associated with ischaemic heart disease.

Table 2 Mean differences in concentrations of lipids between men developing IHD and those not: areas analysed separately

Lipid	*Age-standardised mean differences (95% CI) in lipids between men developing IHD and those not*	
	Caerphilly	*Speedwell*
Cholesterol	0·28 (0·08 to 0·47)	0·30 (0·05 to 0·55)
HDL cholesterol	−0·06 (−0·12 to −0·01)	−0·13 (−0·21 to −0·05)
Triglyceride	0·29 (0·06 to 0·51)	0·35 (0·14 to 0·55)

Abbreviations as in table 1.

In all analyses of the major lipid fractions the data from the two studies were combined. The difference in incidence between the areas due to the different durations of follow up was accommodated by including area as a two level factor in all analyses. This assumes that the relations between incidence of ischaemic heart disease and the major lipids in the two areas are parallel on the logit scale. The assumption was tested by adding interaction terms to the models. No significant interactions were found.

Results

INCIDENCE OF MAJOR ISCHAEMIC HEART DISEASE

A total of 251 major ischaemic heart disease events occurred during follow up; 153 in Caerphilly and 98 in Speedwell. The average annual incidence was 1·2% in Caerphilly and 1·3% in Speedwell. The distribution of the three types of event was similar in the two areas; 50% were fatal, 39% were clinical non-fatal myocardial infarction, and 11% were electrocardiographically defined myocardial infarction.

MEN WITH COMPLETE DATA OR MISSING VALUES

Among the 4641 men who provided a fasting blood sample there were 233 major ischaemic heart disease events. Information was missing on cholesterol concentrations for 79 men, HDL cholesterol concentrations for 119 men, and triglyceride concentrations for 115 men. Sixty four men had missing data for non-lipid risk factors (smoking, body mass index, blood pressure). The univariate analyses are based on all men who had a measurement for each lipid. The multivariate analyses are based on 4371 men with complete data.

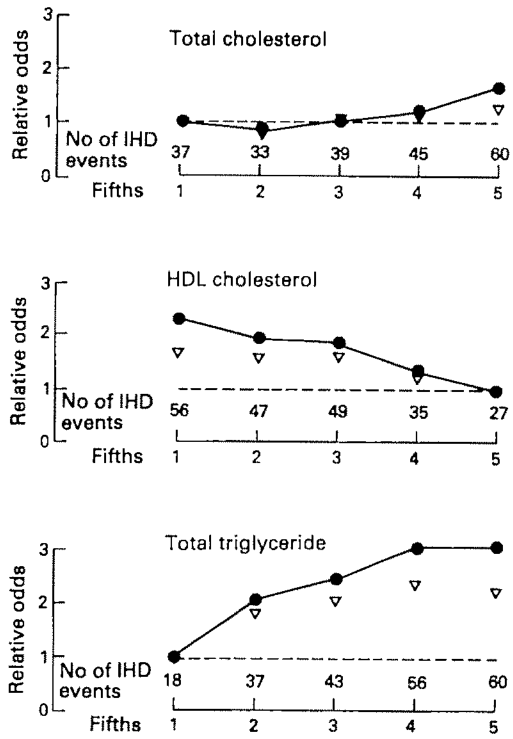
UNIVARIATE ANALYSES

Table 1 shows the mean concentrations of cholesterol, HDL cholesterol, and triglyceride for the men who had a major ischaemic event and for those who did not. The age and area adjusted mean difference and its 95% CI are also given. Total cholesterol and triglyceride concentrations were higher, by 0·29 and 0·31 mmol/l respectively, in men who had an event, and HDL cholesterol concentration was lower, by 0·09 mmol/l. All these differences are significant ($p < 0·001$). Table 2 shows that the age adjusted mean differences of each of these lipids were similar in the two areas. Only for HDL cholesterol concentration was there any appreciable difference between the areas: in Speedwell HDL cholesterol concentration was 0·13 mmol/l lower in men developing ischaemic heart disease, whereas in Caerphilly it was 0·06 mmol/l lower. This difference between the areas is not statistically significant.

Table 3 Correlation coefficients between lipids

	Cholesterol	*HDL cholesterol*
HDL cholesterol:		
Caerphilly	0·03	—
Speedwell	0·04	—
Triglyceride:		
Caerphilly	0·36	−0 24
Speedwell	0·34	−0·28

Triglyceride concentration transformed to natural logarithms. Abbreviation as in table 1.



Relative odds of major ischaemic heart disease with different concentrations of cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride. ■, base group; ●, adjusted for age and area only; ∇, adjusted for age, area, smoking, diastolic blood pressure, body mass index, ischaemic heart disease at recruitment, and the two other major lipids.

INTERRELATIONS BETWEEN LIPID MEASUREMENTS

Table 3 shows correlation coefficients between cholesterol, HDL cholesterol, and triglyceride concentrations. They are given separately for each area, and are similar in the two areas. Association between total cholesterol and HDL cholesterol was minimal, but triglyceride concentration was associated positively with cholesterol concentration and negatively with HDL cholesterol concentration.

RELATIONS WITH OTHER RISK FACTORS

Both cholesterol and HDL cholesterol concentrations showed little association with smoking, age, or blood pressure. Triglyceride concentration was higher by 0·14 mmol/l in smokers than in non-smokers, and showed a small positive association with diastolic blood pressure (r = 0·16 in Caerphilly and 0·11 in Speedwell). Body mass index showed a weak positive association with cholesterol concentration (r = 0·04 and 0·09), but stronger associations with HDL cholesterol (r = −0·17 and −0·23) and triglyceride concentrations (r = 0·27 and 0·26).

Men who had any evidence of pre-existent disease (angina, history of severe chest pain, or ischaemia on electrocardiogram) at recruitment, had higher cholesterol concentrations (by 0·14 mmol/l in both areas), lower HDL cholesterol concentrations (by 0·04 mmol/l in both areas) and higher concentrations of triglyceride (by 0·25 mmol/l in Caerphilly and by 0·19 mmol/l in Speedwell).

MULTIVARIATE ANALYSIS

In the multivariate analysis the relation between incidence of ischaemic heart disease and each of the three major lipid fractions was assessed after adjustment for both the other two fractions and for the non-lipid risk factors, age, smoking, diastolic blood pressure, body mass index, and each of the three types of pre-existent disease.

The figure shows the relative odds of major ischaemic heart disease by "fifths" of the concentration of each lipid variable. Two sets of values are given; one with adjustment for age and area only, the other with adjustment for all non-lipid risk factors and both of the other two lipid fractions. Table 4 shows the standardised relative odds of major ischaemic heart disease with successive adjustment for other variables.

Table 4 Effect of successive adjustment for other risk factors on the standardised relative odds of developing major IHD in relation to total cholesterol, HDL cholesterol, and total triglyceride concentrations

	Standardised relative odds		
Adjusted for	*Cholesterol*	*HDL cholesterol*	*Triglyceride*
Age and area only	1·24**	1·37***	1·41***
All non-lipid risk factors:†	1·17*	1·26**	1·29***
+Cholesterol	—	1·27**	1·25**
+HDL cholesterol	1·18*	—	1·19*
+Triglyceride	1·12	1·22*	—

*p < 0 05; **p < 0·01; ***p < 0·001. Standardised relative odds are the proportionate change in odds for a 1 SD increase in cholesterol and triglyceride, and a 1 SD decrease in HDL cholesterol. Triglyceride transformed to natural logarithms. †Successive adjustment for additional risk factors. Abbreviations as in table 1.

TOTAL CHOLESTEROL

The relative odds value for major ischaemic heart disease in the top 20% of the distribution of cholesterol concentration compared with the bottom 20% was 1·66 (95% CI, 1·10 to 2·52) when adjusted for age and area only. On adjusting for the non-lipid risk factors and for HDL cholesterol and triglyceride concentrations, the relative odds value fell to 1·30 (95% CI 0·82 to 2·06). A major factor in this decline was the adjustment for triglyceride concentration (table 4). The standardised relative odds value for ischaemic heart disease was 1·24 (p < 0·01) on adjustment for age and area only. Adjustment for the other non-lipid risk factors reduced this to 1·17 (p < 0·05). The main reason for the decline was the adjustment for pre-existent disease. Adjustment for HDL cholesterol concentration marginally increased the standardised odds value to 1·18, and the final adjustment for triglyceride concentration caused a further reduction to 1·12. This value was not significantly different from 1·0. The mean difference in cholesterol concentration between men who developed ischaemic heart disease and those who did not declined from 0·26 mmol/l ($p < 0\cdot01$) with adjustment for age and area only, to 0·22 mmol/l ($p < 0\cdot05$) after adjustment for all non-lipid risk factors and HDL cholesterol concentration, and to 0·13 mmol/l (not significant) after the final adjustment for triglyceride concentration.

HDL CHOLESTEROL

The figure shows that relative odds of major ischaemic heart disease increased steadily as HDL cholesterol concentration decreased so that in the lowest 20% of the distribution the value was 2·32 (95% CI 1·46 to 3·67) after adjustment for age and area only, declining to 1·72 (95% CI 1·04 to 2·84) on adjustment for all risk factors. Table 4 shows that the standardised relative odds decreased correspondingly from 1·37 ($p < 0\cdot001$) to 1·22 ($p < 0\cdot05$). The mean difference in HDL cholesterol concentration between men who developed major ischaemic heart disease and those who did not was −0·10 mmol/l ($p < 0\cdot001$) on adjustment for age and area only, decreasing to −0·06 mmol/l ($p < 0\cdot05$) on adjustment for all other factors. The association between HDL cholesterol concentration and incidence of ischaemic heart disease was unchanged with adjustment for cholesterol concentration and declined slightly on further adjustment for triglyceride concentration (table 4). The fully adjusted standardised relative odds value of 1·22 was both significantly greater than 1·0 and higher than the non-significant value of 1·12 for total cholesterol concentration.

TOTAL TRIGLYCERIDE

Figure 1 shows that the relative odds of major ischaemic heart disease rose as triglyceride concentration increased, to a value of 3·10 (95% CI 2·25–6·17) in the top 20% of the distribution. On adjustment for all other factors this decreased to 2·26 (95% CI 1·26 to 4·05). Table 4 shows that the standardised relative odds declined steadily with each successive adjustment from 1·41 ($p < 0\cdot001$) with adjustment for age and area only to 1·19 ($p < 0\cdot05$) with adjustment for all other factors. The mean difference in triglyceride concentration between men who developed ischaemic heart disease and those who did not showed the same pattern.

The decline both in standardised relative odds and mean differences with each successive adjustment was steeper for triglyceride than for either cholesterol or HDL cholesterol concentration. The standardised relative odds value of 1·19 after adjustment for all other factors was, however, like that for HDL cholesterol concentration, both statistically significant ($p < 0\cdot05$) and larger than the odds associated with total cholesterol concentration.

Table 5 Mean differences in concentrations of lipids between men with and without incident IHD according to IHD status at recruitment*

	No pre-existent IHD† *(n = 3350)*	*Any pre-existent IHD* *(n = 1021)*
Cholesterol (mmol/l)(95% CI)	0·15 (−0·07 to 0·38)	0·29 (0·04 to 0·53)
HDL cholesterol (mmol/l) (95% CI)	−0·08 (−0·15 to −0·01)	−0·07 (−0·14 to 0·00)
Log triglyceride (mmol/l) (95% CI)	0·17 (0·07 to 0·26)	0·09 (0·00 to 0·19)

*Mean differences are adjusted for all non-lipid risk factors.
†Pre-existent IHD includes angina or history of severe chest pain from the chest pain questionnaire or evidence of ischaemia on electrocardiogram. Abbreviations as in table 1.

EFFECT OF PRE-EXISTENT DISEASE

Of the 251 major ischaemic heart disease events among the total cohort of 4860 men, 131 events occurred among the 1171 men with ischaemic disease at recruitment. The age and area adjusted relative odds value for a major event for men with pre-existing disease was 3·61 (95% CI 2·77 to 4·70) compared with men with no disease at recruitment. Men with pre-existent disease had higher concentrations of cholesterol and triglyceride and lower concentrations of HDL cholesterol at recruitment. In theory, associations between each of the three lipids and the incidence of ischaemic heart disease could arise simply as a consequence of pre-existent disease. The multivariate analysis, which includes an adjustment for the three types of pre-existent disease, shows that this is not the case, and table 5 confirms this. Mean differences in the three lipids between men who developed major ischaemic heart disease and those who did not are shown separately for men with and without pre-existent disease. For both HDL cholesterol and triglyceride concentrations the differences were larger for men with no evidence of disease at recruitment. All mean differences were significantly different ($p < 0\cdot05$) from zero except those for total cholesterol for men without pre-existent disease which, however, did not differ significantly from the corresponding difference in men with pre-existent disease.

EFFECT OF β BLOCKADE

As one of the items in the medical history, the men were asked whether they had taken any prescribed medicines in the past seven days. The names of all medicines were recorded. Of the total cohort of 4860 men, 245 (5·0%) were taking β blockers. These had been prescribed for 148 (12·6%) of the 1171 men with pre-existent ischaemic heart disease, compared with 97 (2·6%) of the 3689 men without pre-existing disease. Thirty three major ischaemic heart disease events occurred among the 245 men taking β blockers, giving an incidence of 13·5%. This compares with 218 (4·7%) events among the 4615 men not taking β blockers. The higher incidence among the men taking β blockers reflects the fact that they are a selected, high risk group.

The men taking β blockers had substantially different lipid concentrations from those not taking the drug. Total cholesterol concentrations were higher by 5%, total triglyceride concentration was higher by about 30%, and HDL cholesterol concentration was lower by 10%. The effect of β blockade on the relations between lipids and incidence of disease was therefore examined.

There was no evidence that the difference in lipid concentrations between men who had a major incident and those who did not varied according to whether or not they were taking β blockers. Formally, interaction terms added to the multiple regression models of table 1 were not significant. Mean differences in lipid concentrations adjusted for age, area, and β blockade were 0·26 mmol/l, −0·08 mmol/l, and 0·27 mmol/l for total cholesterol, HDL cholesterol, and total triglyceride concentrations respectively. These were all slightly smaller than the corresponding differences shown in table 1.

The analysis given in table 4 was also repeated with additional adjustment for β blockade. The fully adjusted standardised relative odds values were unchanged for total cholesterol and triglyceride concentrations. For HDL cholesterol concentration the value was marginally reduced, from 1·22 to 1·21.

Discussion

The results from the Caerphilly and Speedwell studies confirm that concentrations of cholesterol, HDL cholesterol, and triglyceride are associated with the development of major ischaemic heart disease. Questions about their relative importance remain, however. The only other large prospective British study that has considered this in detail concluded that concentration of triglyceride was not an independent risk factor and that cholesterol was a more important risk factor than HDL cholesterol concentration.[7] Our results suggest the opposite.

The Regional Heart Study found that triglyceride concentration did not predict incidence of ischaemic heart disease once other risk factors had been taken into account.[7] This accords with other published views,[8 19] but the evidence is not consistent. For example, Carlson *et al* found in the Stockholm Study that after allowing for age, blood pressure, and smoking, plasma triglyceride concentrations were more strongly predictive than was cholesterol.[20] This corresponds with our findings.

Some studies including ours were based on fasting triglyceride concentrations whereas others, such as the Regional Heart Study, measured non-fasting concentrations. Non-fasting samples contain higher and more variable concentrations of triglycerides than do fasting samples because of the presence of chylomicrons when not fasting. It is debatable whether fasting or non-fasting samples are more appropriate. One advantage of fasting samples is that all subjects are in the same metabolic state. On the other hand, subjects spend most of the day in the postprandial state. Unfortunately, it is impossible with a large free living cohort to draw a blood sample at a standard time after a typical meal, even if a typical meal for each subject could be defined.

Another aspect of this debate has recently been raised by Davey Smith and Phillips.[21 22] It is well known that random errors in a putative risk factor result in underestimation of regression coefficients and hence of relative odds. Davey Smith and Phillips show that when considering whether a risk factor is independently associated with a disease, after adjusting for a confounding variable with which it is highly correlated, the relative sizes of the random error in the estimation of the risk factor and the confounder may be very important. Such random error would include both measurement error and intraindividual variation. In particular, Davey Smith and Phillips suggest the possibility that differential random error could induce the common finding that the univariate association between triglyceride concentration and ischaemic heart disease largely disappears on adjustment for HDL cholesterol concentration whereas the association between HDL cholesterol concentration and ischaemic heart disease remains on adjustment for triglyceride concentration. This could explain the apparent inconsistency between the Regional Heart Study and our studies. The Regional Heart Study measured non-fasting triglycerides and our studies measured fasting concentrations. Thus the random error in the triglyceride concentration relative to that in the HDL cholesterol concentration is likely to be substantially smaller in our studies. It seems unlikely, however, that the general inconsistency between studies can be so explained because studies that claim no independent role for triglyceride include not only those based on non-fasting samples[7] but also others based on fasting samples.[8 19]

Early reports from the Framingham Study suggested that triglyceride is not an independent risk factor for men.[23] A more recent report found that it is a risk factor in men with low concentrations of HDL cholesterol.[9] We found no evidence for such an interaction. Incidence of ischaemic heart disease increases with increasing triglyceride concentration at all concentrations of HDL cholesterol. For example, if the distributions of both variables are divided into thirds, then the unadjusted odds of ischaemic heart disease for men who are in the top third of the triglyceride distribution relative to those in the bottom third are 2·1, 2·0 and 3·1 respectively within the low, middle, and top thirds of the distribution of HDL cholesterol.

Initially, the Regional Heart Study reported that HDL cholesterol was not a major risk factor for the disease in British men.[6] A later report revised that view and concluded that it was important,[7] but less so than cholesterol, which was the most important single blood lipid risk factor in men. In our data, the standardised relative odds value for HDL cholesterol concentration after adjusting for age, blood pressure, smoking, body mass index, pre-existing disease, and total cholesterol was 1·27, compared with a value of 1·18 for total cholesterol concentration adjusted for the same non-lipid risk factors and HDL cholesterol concentration. The standardised relative odds value of 1·27 for HDL cholesterol concentration is similar to the figure of 1·30 found by the Regional Heart Study.[7] The corresponding adjusted mean difference of −0·07 mmol/l between men who developed ischaemic heart disease and those who did not is also close to the

Regional Heart Study's value of −0·06 mmol/l. The review paper of four American prospective studies showed that after adjustment for a similar set of risk factors, a 1 mg/dl (0·026 mmol/l) decrease in HDL cholesterol concentration was associated with proportionate increases of 1·9%, 2·1%, and 2·3% in odds of a major ischaemic heart disease event in the Framingham Study, the Multiple Risk Factor Intervention Trial, and the Lipid Research Clinics Coronary Primary Prevention Trial respectively.[5] The corresponding figure for the Caerphilly and Speedwell Studies is 2·1%. Thus substantial agreement exists between these studies on the strength of the association between HDL cholesterol concentration and incidence of ischaemic heart disease.

The reason that the relative importance of HDL cholesterol and cholesterol concentrations is opposite to that found by the Regional Heart Study is because the association between cholesterol concentration and incidence of disease is less strong in our studies. The standardised relative odds value of 1·18 from table 4 compares with a value of 1·54 from the Regional Heart Study. Similarly, adjusted mean differences in total cholesterol concentrations between men who developed ischaemic heart disease and those who did not are about half the value of 0·46 mmol/l found by the Regional Heart Study.

β Blockers are known to affect the lipoprotein profile. Cruickshank concludes that triglyceride concentration is increased by 20–30%, and HDL cholesterol concentration is decreased by 10%, but that plasma total cholesterol concentration is unchanged.[24] In our study, the men taking β blockers had triglyceride and HDL cholesterol concentrations that differed by almost the same percentages. The number of men taking β blockers was small, 245 (5%) of the total cohort of 4860 men, but they were a highly selected group with a high incidence of major ischaemic events. The age and area adjusted relative odds value for a major incident event among men taking β blockers was 2·86 (95% CI 1·88 to 4·36) compared with men not taking the drugs.

Therefore it is possible that part of the association between, particularly, triglyceride concentrations and incidence of disease is an artefact, arising because a group at high risk is taking a drug that substantially inflates their triglyceride concentration. This is not the case, however. The increased triglyceride concentrations in men who go on to develop major disease are found both in those groups taking β blockers and in those not taking β blockers. Table 1 shows that in the cohort as a whole, the men who had a major event had triglyceride concentrations that were 0·31 mmol/l higher. Among men not taking β blockers, the corresponding increase in triglyceride concentration was 0·29 mmol/l. Again for triglyceride concentration, the standardised relative odds value for a major event is 1·19 after adjusting for all the non-lipid risk factors and both cholesterols (table 4). When this analysis is restricted to the men not on β blockers the standardised relative odds value increases slightly to 1·21.

Thus the association between triglyceride concentration and incidence of major ischaemic heart disease is independent of the role of β blockers. The fact that in this large cohort of men the association is stronger than that with plasma total cholesterol concentration calls for a re-evaluation of the role of triglyceride concentration in ischaemic heart disease.

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Proceedings of the British Cardiac Society

The 1992 Annual General Meeting of the British Cardiac Society was held at the Harrogate International Conference Centre from 26 to 29 May.

The President, Dr D A Chamberlain, took the Chair during private business. Dr J G F Cleland was elected as Assistant Honorary Secretary, and Dr D Dymond took over as Honorary Secretary from Dr P Oldershaw. Dr R Boyle was elected to Council on the retirement of Prof R W F Campbell.

Deaths during the year:
W T Brandt, J S Fleming, S Oram, L Schamroth, Sir Horace Smirk, M Suzman, R J Vakil, P Yu.

New Members 1992:
R I Bain (Grimsby); R Blackwood (Wexham); N Cary (Cambridge); K Chan (Leicester); M Cheesman (Wesbury on Trym); M Colquhoun (Hereford); G Dalzell (Londonderry); J W Dean (London); M de Belder (London); J Dyet (Hull); J Francis (Stafford); R Franklin (Harefield); M Griffith (Newcastle); L Hughes (London); R Jeffrey (Aberdeen); G Kaye (Leeds); D Kitchiner (Liverpool); E Ladusans (Manchester); D Maciver (Birmingham); J M Morgan (London); J Murphy (Darlington); D Northridge (Cardiff); J Polonieck (London); M Pye (London); A Shah (Cardiff); J Smyllie (Leeds); U Somasundram (Northallerton); J Stewart (London); D Thompson (Leicester); J Weil (Leeds); F Wells (Cambridge); P Whincup (London); U Wijayawardhana (Lincoln); C Wilson (Belfast); C Wren (Newcastle); A Zezulka (Leeds).

New Corresponding Member:
Prof M Sekiguchi (Japan)

The following are abstracts of the papers that were presented.

Clinical and echocardiographic survey of valvar and myocardial disease in a representative sample of elderly people in the general population

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To measure the frequency of valvar and myocardial disease in the elderly (> 64) general population, an age and sex stratified random sample of Southampton residents was asked to answer a standard questionnaire and have a physical and echocardiographic examination. Clinical data (28 demographic, 82 symptom, and 96 physical variables for each subject) were collected from 259 people (a response rate of 64%). In 236 (131 men) a full echocardiographic data set (56 variables) was obtained. Symptoms of possible cardiac origin or abnormal physical cardiac findings or both were present in 197 (83%(100 men)), 170 (72%(84 men)), and 111 (47%(51 men)), respectively. The clinical diagnoses were aortic stenosis in four women (2%), aortic regurgitation in 13 (5·5%(six men)), mitral regurgitation in 13 (5·5%(7 men)), mitral stenosis in one woman (1%), tricuspid regurgitation in five (2%(two men)), congestive cardiac failure in six (2·5%(two men)) and hypertension in 33 (14%(19 men)). Echo and Doppler abnormalities or both, found in 105 (44%(55 men)) of which 10 were unsuspected clinically, were aortic stenosis in six (2·5%(two men)), aortic regurgitation in 35(14%(15 men)), mitral regurgitation in 16 (6%(seven men)), mitral valve prolapse in two men (1%), tricuspid regurgitation in 15 (6%(five men)), cardiomyopathy in one man (0·5%) and atrial septal defect in seven (3%(five men)). Those with cardiac symptoms and signs were older (mean age 74·1 (range 65–99) *v* 71·1 (65–87)), of lower social class (87 of 105 in the lowest three classes), and had a high frequency of smoking (37/48), hypertension (74/78), and diabetes (13/14). Overall the positive and negative predictive values (with respect to echo) of cardiac symptoms were 0·43 and 0·54, of cardiac signs 0·51 and 0·73, and of either or both 0·48 and 0·74 respectively.

Thus in the elderly, the prevalence of valvar and myocardial disease may be as high as 44%, 9·5% of which may not be clinically manifest.

Cost-benefit analysis of radiofrequency catheter ablation for cure of supraventricular arrhythmias

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Radiofrequency catheter ablation is becoming established as an effective treatment for physiological cure of supraventricular arrhythmias involving an extra pathway, such as those associated with the Wolff-Parkinson-White syndrome and atrioventricular (AV) nodal re-entrant tachycardia. All new procedures have cost implications, and we have tried to assess these for this new procedure in comparison with medical management or specific arrhythmia surgery. In the last year, specific ablation has been attempted in 53 patients (mean age 30) with extra pathways (47 with accessory AV pathways, six with slow AV nodal pathways) with an overall success rate of 39/53 (74%). Our overall surgical success rate is > 95%. Surveying 20 consecutive ablation patients, there were eight emergency in patient admissions for tachycardia in the year before ablation, with a total of 30 days spent in hospital as a result, and 11 other visits to a casualty department. The annual costs for a medical patient include the cost of drugs (mean 1·25 drugs/patient at any one time), using the cost of flecainide (the drug most frequently taken by the patients) as the index, and two routine out patient visits with electrocardiograms per year plus the cost of emergency care. Catheter ablation and surgical costs include the cost of the failures. Successfully treated patients were discharged after a single follow up. Surgical costs include the cost of prior electrophysiological study, but this is not included in catheter ablation costs as it is now our practice to combine electrophysiological study with ablation, and costs have been calculated on this basis. In 1991, relative costs of catheter ablation and medical treatment were 4·2:1, and surgery in comparison with catheter ablation was 2·1:1.

Surgical patients returned to work an average of 70 days after operation, whereas catheter ablation patients returned to work within an average of five days.

Catheter ablation offers immediate cost benefits to surgery, and cost benefits in comparison with medical treatment over a five year period. As the average age was only 30, and the patients had otherwise normal life expectancy, ablation offers good cost benefits overall.

Confidential enquiry into cardiac catheter complications

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The confidential enquiry into cardiac catheter complications (CECCC) is a voluntary audit of such complications set up under the joint auspices of the British Cardiac Society and the Royal College of Physicians. Data collection started in August 1990 with a pilot study in five centres. By November 1991 16 centres were participating. The total number of registered patients (on 30 November 1991) was 18 734. Of these, 16 577 had undergone diagnostic cardiac catheterisation and 2165 percutaneous coronary angioplasty. In centres undertaking adult cardiology left heart catheter and coronary angiography accounted for a mean of 85% of all studies, but in one centre the proportion was only 64%. In centres undertaking percutaneous coronary angioplasty the median ratio of coronary angioplasty to coronary angiographic studies was 1:4·5. 220 complications (defined as untoward events that threatened life or prolonged hospital stay) were registered. The complication rate for diagnostic angiography was 0·93% and for coronary angioplasty 3·00% (unsuccessful angioplasty was not, in itself, a complication). Mortality was 0·11% for diagnostic angiography and 0·23% for percutaneous coronary angioplasty. These results (which may represent the results of selected well organised and well motivated centres) compare well with recent data from the United States.

Analysis of individual complications showed noticeably different patterns between centres, which may reflect differences in cathether techniques. Feedback to the centres concerned has been provided. Confidential enquiry into cardiac catheter complications provides a framework for audit, and for continuing research on ways of further reducing catheter morbidity.

Coronary bypass: a district general hospital's perspective

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We reviewed the experience in our hospital of surgery for obstructive coronary artery disease for a six year period ending December 1989. During this time a series of 101 consecutive patients from our district general hospital underwent coronary artery bypass grafting at the regional cardiothoracic centre. Our hospital has one cardiologist and seven physicians, all of whom participate in emergency receptions. Patients admitted to the coronary care unit remain the responsibility of the admitting consultant and are seen by the cardiologist on request. The cardiologist has full access to the facilities at the regional cardiothoracic centre. There was a wide variation between individual physicians in the numbers of patients referred for cardiological evaluation who ultimately underwent coronary artery bypass surgery (range 2 to 11). Patients admitted during physician receptions were about half as likely to receive surgery when compared with patients admitted on the cardiologist's receptions. This was a relatively young series of patients with a mean age of 56 (range 33 to 76) with advanced coronary artery disease; 19% left main coronary artery stenosis and 72% three vessel coronary artery disease in those without left main stem disease. The group had severe symptoms reflected by a 36% incidence of emergency surgery for refractory unstable angina and with patients taking a mean of 2·5 (range 0 to 3) anti-anginal drugs at the time of angiography. Emergency procedures accounted for 46% of operations performed. Operative results were good especially when the severity of disease and the high proportion of emergency operations is considered; there was a 4% operative mortality with 63% of patients well and taking no regular anti-anginal treatment at a mean follow up of five years.

We conclude that surgery provided an effective treatment for this selected group of high risk patients with coronary artery disease. The wide variation between different physicians in the number of patients referred who progressed to bypass grafting and the fact that patients admitted on a physician's reception were less likely to undergo bypass surgery suggests, however, that some patients who would have benefited from surgery may have been denied this form of treatment.

Monitoring cardiac arrest management in an accident and emergency department with a video camera

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Assessment of the resuscitation skills of medical and nursing staff, by questionnaires, manikins, and simulated cardiac arrests, has shown deficiencies that may reduce the chances of successful outcome. Video material is already used as a teaching aid to demonstrate ideal cardiac arrest management. We describe the use of a video camera as part of an audit of true cardiac arrests. The camera is placed in the resuscitation room of the accident and emergency department to provide a fixed field of view, and a microphone is positioned conveniently. The system is activated before the arrival of expected collapse cases brought in by ambulance, to record the preparation of equipment and the management of the resuscitation attempt. Personnel who have taken part in the resuscitation are encouraged to watch the tape recording, informally, with a senior member of staff, before it is wiped clean after a week. A review of the first 10 cases showed deficiencies both of an individual nature (improper rate of chest compressions,, improper defibrillator technique), and of a general nature (poor organisation, overcrowding of the resuscitation room, and prolonged interruptions in cardiac massage).

In future it will be possible to develop simultaneous electrocardiographic recording to assess arrhythmia recognition, an automatic switch on device to maximise cases recorded, and multiple cameras to provide views of the whole room. The system will become a useful audit tool leading to improved resuscitation skills.

The effect of cardiac catheterisation facilities on the rate of coronary artery bypass grafting in Scotland

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In Scotland, in 1988, the Scottish Home and Health Department set a target of 350 coronary bypass operations/million/year and achieved a rate of 345 in 1990 (OPCS4 K40–46). There are 12 Health Boards in mainland Scotland. The rate of coronary bypass surgery ranged from 254/million (Dumfries) to 415/million (Greater Glasgow). The mortality from ischaemc heart disease (ICD 410–414) ranged from 318/100 000 (Lothian) to 420/100 000 (Dumfries and Galloway). There was no relation between the death rate from ischaemic heart disease and the rate of coronary bypass surgery. Four Health Boards (all teaching centres) have facilities for cardiac catheterisation and of these three perform coronary bypass surgery. In 1990 the rate of cardiac catheterisation (OPCS4 K63 and K65) ranged from 80/100 000 (Highland) to 171/100 000 (Grampian). There was no relation between death rate from IHD and rate of cardiac catheterisation. Rate of cardiac catheterisation and coronary bypass surgery correlated strongly (R = 0·8). The population of the four Health Boards performing cardiac catheterisation was 2,573,715 *v* 2,437,910 in the remaining eight Health Boards; the mortality from ischaemic heart disease was similar—352 *v* 363/100 000. The rate of cardiac catheterisation was 55% higher in those four Health Boards which performed this (144 *v* 93/100 000). The rate of coronary bypass surgery was 43% higher (387 *v* 271/million).

The rate of cardiac catheterisation is a major determinant of the rate of coronary bypass surgery. If those Health Boards which did not achieve the Scottish Home and Health Department target for coronary bypass surgery wish to do so, then this will require them to appoint more cardiologists with facilities for the full investigation of patients with ischaemic heart disease.

Balloon dilatation of the aortic valve for severe symptomatic aortic stenosis in early infancy: the treatment of choice?

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Severe aortic stenosis in the neonatal period has a high mortality, even with prompt surgical treatment. During a 2·5 year period, 10 consecutive infants with severe aortic stenosis have been treated by balloon dilatation of the aortic valve. All patients were symptomatic at <6 weeks of age, eight in the first week. Associated abnormalities included coarctation of the aorta in five patients (severe in three, mild/moderate in two), complete atrioventricular septal defect one patient, severe mitral regurgitation one patient, and endocardial fibroelastosis in seven patients (severe in three). A percutaneous approach via the femoral artery was used with a valvoplasty balloon of diameter equal to or 1 mm less than the aortic annulus diameter measured echocardiographically. Coexisting severe coarctation was treated by balloon dilatation of the aorta in two patients and surgical repair in one patient. Symptomatic improvement with return of peripheral pulses and improvement of heart failure occurred in eight patients (80%). Two patients died despite adequate dilatation shown at post mortem examination. One had severe left ventricular hypoplasia, the other a very dysplastic valve. Later death occurred in three patients with associated cardiac abnormalities (one atrioventricular septal defect, one mitral regurgitation, one endocardial fibroelastosis + coarctation). Necropsy in two patients showed relief of commissural fusion. Complications included guide wire perforation of the left ventricle in one patient and loss of femoral pulse in four patients. The presence of associated abnormalities and the degree of left ventricular hypoplasia were the main determinants of survival. Only 1/6 patients with a left ventricular diastolic diameter of <2·0 cm survives. The four patients with left ventricular diastolic diameter >2·0 cm are alive and well. The five survivors (50%) have been followed up for two to 24 (mean 13) months. Four are asymptomatic and have mild to moderate residual aortic stenosis; one with severe endocardial fibroelascosis requires diuretic therapy.

Balloon dilatation of the aortic valve offers a promising alternative to surgical valvotomy in infants with severe aortic stenosis. Coarctation frequently coexists and may also be treated by balloon dilatation.

Balloon dilatation for aortic stenosis: age at presentation is an important determinant of the outcome

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Balloon dilatation of the aortic valve was attempted in 38 children over a five year period. The age at presentation was <1 week in nine, <1 month in five, 1 month to 1 year in eight, and >1 year in 16. Of the nine patients presenting <3 days of age, there were no survivors. All presented with severe congestive cardiac failure, required a prostaglandin infusion, and had endocardial fibroelastosis. In three of these, procedural complications contributed to the fatal outcome: arterial damage in two and left ventricular perforation in one. The other six all died between 1 and 185 days after balloon dilatation from left ventricular dysfunction despite technically successful dilatations (augmented by surgical valvotomy in two). A successful outcome was obtained in four of the five patients treated between one and four weeks of age: they now have Doppler gradients between 25 and 50 mm Hg at a follow up of 1 to 2 years though one also required a surgical valvotomy. The fifth patient died of congestive failure 10 days after balloon dilatation. Of the eight patients treated between one month and one year of age, four are well palliated (one after a second balloon dilatation). There was one procedural death due to an anaesthetic complication. Surgery was performed in three patients: two after a second balloon dilatation and one urgently after valve disruption. Of the 16 patients treated after the first year of life, two had previously undergone a surgical valvotomy. The immediate transvalvar gradients after balloon dilatation fell from a mean of 67 mm Hg (range 40 to 105) to a mean of 27 mm Hg (range 10 to 40). One patient required a further balloon dilatation. There has been no mortality or need for surgery in any of these patients. The Doppler estimated gradients ranged from 22 to 60 mm Hg after follow up from two months to four years.

Balloon dilatation of critical aortic stenosis in neonates is accompanied by a high mortality due to arterial complications and associated left ventricular dysfunction. Presentation beyond the first week of life is associated with a better outcome and prognosis. In patients >1 year of age balloon dilatation is an effective and safe palliative procedure that can delay the need for, and supplement, surgery.

Comparison of balloon dilatation, laser-balloon dilatation and stent implantation for maintaining patency of the arterial duct

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In children with duct dependent cyanotic heart disease, maintenance of patency of the arterial duct by transcatheter techniques, could replace neonatal systemic to pulmonary artery shunt operations. We have evaluated the relative efficacy of balloon dilatation, laser "hot" balloon dilatation, and stent implantation for this purpose in 30 newborn lambs (age 4·4 (1·7) days: weight 4·6 (1·2) kg). In three lambs, it was not possible to recanalise the duct. In seven, balloon dilatation (with 4–10 mm balloons) alone and in two, laser balloon dilatation (2·5 and 3 mm laser balloons) was performed. Stent implantation alone was performed in seven (four with additional balloon dilatation) using balloon expandable or self expanding stents of 4–8 mm diameter, and 11 underwent sequential balloon dilatation and stent implantation with the same size device (4–6 mm). After balloon dilatation alone, the duct size averaged 40–50% of the balloon diameter. Within five minutes of balloon dilatation, however, the duct had either closed or constricted to a diameter of less than 1 mm in four and less than 2 mm in a further two. The only inflation to 10 mm after a poor result at 8 mm ruptured the duct producing tamponade. Laser balloon dilatation alone produced patent ducts of only 1–1·5 mm. Stent implantation produced well defined ducts with diameters of at least 80–90% of the stent diameter. In those undergoing sequential balloon dilatation and stent implantation with similar sized devices, there was a rise in the pulmonary to systemic pressure ratio from 0·31 (0·1) at baseline to 0·41 (0·1) after balloon dilatation and to 0·57 (0·2) after stent implantation ($p < 0{\cdot}001$). The pulmonary to systemic flow ratio increased from 2·2 (1·0) after balloon dilatation to 3·5 (2·1) after stent implantation ($p < 0{\cdot}05$). The duct diameter at angiography increased from 0 mm at baseline to 2·1 (1·3) mm after balloon dilatation and to 4·7 (1·0) mm after stent implantation ($p < 0{\cdot}001$).

Stent implantation with 4–6 mm devices, consistently produces better haemodynamic and angiographic patency of the arterial duct than balloon or laser balloon dilatation alone. Long term studies of its efficacy are warranted.

Long-term results of stent implantation for maintaining patency of the arterial duct

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Stent implantation has been shown to be superior to balloon dilatation in achieving widely patent and regular channels, either as an adjunct to or in place of balloon dilatation, in both peripheral and coronary artery disease. To investigate the possibility that stent implantation into the arterial duct could replace neonatal systemic to pulmonary artery shunt operations we implanted stents (Wallstent, Tower or Palmaz-Schatz) into the arterial ducts of 15 newborn lambs (age 2 to 7 days, weight 3 to 7·3 kg). Within 4 to 10 days of stent implantation the duct was closed or virtually closed in five. In all of these the stents had been placed so that 1 to 2 mm of the aortic end of the duct had not been stented. In three of these the stents could not be visualised at the time of implantation due to poor radio-opacity (Palmaz-Schatz stents). In one, the duct was barely patent (Tower) and in one the stent had passed through an intimal tear at the aortic orifice (Wallstent). The first was redilated and the second had an additional overlapping stent implanted. Three lambs died within 48 hours of the procedure and in these the duct was found to be patent. In seven lambs (four with Wallstents and three with Tower stents), follow up now extends to 10 months (median 7·5 months; current weight 10 to 60 kg) and in these the ducts have remained patent. In one, who died six months after stent implantation, from unrelated causes, the duct was investigated by angioscopy. The stent in the duct itself was completely covered by a thin layer of endothelium while a 1 mm portion of the stent protruding into the aorta was free from thrombus or neo-endothelium formation. At the pulmonary end a non-occlusive fibrous narrowing was beginning to form.

Arterial duct patency can be maintained in the long term but to achieve this the implanted stents must span the entire duct length. Stent implantation into the arterial duct may become a viable alternative to neonatal systemic to pulmonary artery shunt operations.

Maintenance of ductal patency by percutaneous stent implantation: early experience

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Balloon expandable stainless steel stents (Johnson and Johnson) were deployed in the arterial duct in four neonates with duct dependent circulation. Two had pulmonary atresia with right sided aortic arch and left sided duct and two had left heart hypoplasia. The stents were mounted upon 3·5 to 4 mm (pulmonary atresia) or 7 mm (hypoplastic left heart) diameter balloon angioplasty catheters and were delivered using the femoral venous, femoral arterial, or axillary arterial approach under general anaesthetic. Repeated procedures were necessary to stent the full length of the ducts in pulmonary atresia; two stents (7 mm and 15 mm length) were required in one case and four (one 15 mm and three overlapping 7 mm stents) in the other. In hypoplasia of the left heart two stents were required in one child and a single stent in the other. Complications included guide wire perforation of a pulmonary artery (treated conservatively), cardiac tamponade (treated by pericardicentesis and autotransfusion), and transient loss of cardiac output. Of those with pulmonary atresia one baby died after five weeks of uncertain cause and the second died of pneumococcal septicaemia after nine days. One baby with hypoplastic left heart died two weeks after stenting, due to sepsis and right heart failure and the other is alive and well after one month. At necropsy the ducts were patent and endothelialisation was nearly complete after five weeks.

Stenting of the arterial duct may allow successful maintenance of patency and merits further study.

Effect on overall outcome of the introduction of balloon dilatation of native aortic coarctation in infants and children

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Since May 1990, 33 neonates, infants, and children presenting with native aortic coarctation and normal cardiac connections were considered for percutaneous balloon dilatation. Twenty four subsequently had balloon dilatation of the coarctation but nine were referred for surgery. The outcome in terms of mortality, complications, and recoarctation (assessed by clinical evaluation, Doppler echocardiography, magnetic resonance imaging, and the need for further procedures) in these 33 children (group A) was compared with that in the 21 consecutive children treated surgically for coarctation between January 1989 and May 1990 (group B). There were 16/33 (48%) neonates in group A and 11/21 (52%) in group B. The median age was 26 days and the median weight 3·7 kg for group A and 32 days and 3·6 kg for group B. In 16 neonates in group A, there were five (31%) deaths and in group B, two (18%) neonates died. Two of these deaths in group A were related to balloon dilatation and one to primary surgical repair, whereas in group B, one death was related to surgery. In patients older than one month, there were no deaths in group A and one death in group B occurred at surgical repair of recoarctation and resection of subaortic stenosis. Of the neonates, four (25%) in group A and three (27%) in group B developed recoarctation. Of those patients older than one month, two (12%) in group A and one (10%) in group B developed recoarctation. Three additional patients in group A and one patient in group B have mild recoarctation on magnetic resonance imaging but have not needed any intervention. No aneurysms have been detected by magnetic resonance imaging in either group.

Balloon dilatation is an acceptable alternative to surgical repair of native coarctation in infants and children, but its role in neonates remains controversial. Nevertheless, some older neonates may derive medium term benefit from balloon dilatation.

Malposition of the Rashkind double umbrella as a cause of residual flow after transcatheter occlusion of the arterial duct

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The lateral aortograms obtained before and after implantation of a single Rashkind arterial duct occluder were reviewed in 121 patients. The position of the occluder within the duct, the disposition of its prongs, and any distortion of the duct from its original shape were noted. Twelve cases were identified in which the distal prongs of the occluder distorted the ampulla or body of the duct in such a way as to splint it more widely open than before implantation. In five patients this could be attributed to technical deficiencies but the shape of the duct contributed to malposition in seven. Outcome of the procedure in terms of achieving complete occlusion confirmed by Doppler echocardiography and the requirement for a second occluder was then compared between cases in whom malposition was present and those in whom the occluder position was optimal. Five (42%) of the 12 ducts with malposition were completely occluded compared with 75/109 (69%) of those with optimum occluder position. Moreover, 5/12 (42%) of those with malposition have residual flow beyond four months after implantation compared with only 14/109 (13%) of those with optimum position. Four (33%) with malposition and 10 (9%) without malposition have had implantation of a second occluder.

Malposition of the Rashkind occluder makes a significant contribution to residual patency of the duct. If, in the setting of malposition of the occluder complete occlusion does not occur early after implantation, then persistent residual leak can be predicted and a second device should be implanted.

Factors influencing the late results of transcatheter occlusion of patent arterial duct with an umbrella device

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The influence of the morphology of the arterial duct, the position and size of the umbrella device, and the time after implantation on the incidence of residual patency was investigated in 125 patients who had undergone arterial duct occlusion using the Rashkind device. The shape of the duct, assessed on the lateral aortogram, was classified into one of five categories: (*1*) broad funnel, (*2*) short (no ampulla), (*3*) parallel tubular, (*4*) tubular with narrow pulmonary end, and (*5*) complex. 63/125 (50%) ducts were classified as type 1, 14 (11%) type 2, 21 (17%) type 3, 23 (19%) type 4, and 4 (3%) type 5. The duct was classified into one of three categories: (*A*) $\leqslant 3$ mm, (*B*) >3 mm $\leqslant 6$ mm, (C) >6 mm. The ducts were in category A in 103 (82%), B in 21 (17%), and C in one (1%). The incidence of complete occlusion for each shape and size of the duct was evaluated. For category A, the occlusion rates were: type 1 = 39/53 (73·5%), type 2 = 8/12 (67%), type 3 = 6/13 (56%), type 4 = 17/23 (73%), and type 5 = 2/2 (100%). The rates of occlusion for category B were: type 1 = 5/10 (50%), type 2 = 1/1 (100%), type 3 = 6/8 (75%), type 4 = 1/2 (50%). The single type 1 duct in category C had a residual leak. Of 41 ducts with residual leak, the position of the occlusion device was suboptimal in eight and optimal in 33 and the size of the device was inappropriate in seven. Of 84 ducts with no residual leak at the latest follow up, 32/84 (38%) were completely occluded on the immediate postimplantation aortogram, and 58/84 (69%) were occluded when assessed by Doppler echocardiogram the next day. The remaining 26 (31%) were first assessed as completely occluded between six weeks and two years later (median = six months).

Small ducts are associated with a higher incidence of complete occlusion but duct shape also influences the results. Malposition and inappropriate size of the occluder are important causes of residual leak. There is a continuing incidence of closure of residual patency with time.

Enhanced myocardial resistance to hypoxia after heat stress is dependent on metabolic substrate

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When any living cell is exposed to sub-lethal temperature increase a series of adaptive changes occur which serve to protect that cell from subsequent increases in temperature.

A group of proteins known as the heat stress proteins are the only proteins translated during such stress and play a pivotal role in providing this protection. In the heart a wide variety of insults other than heat stress, such as ischaemia also result in heat stress protein synthesis. In the buffer perfused rabbit heart, heat stress enhances contractile function after ischaemia and reperfusion. The physiological basis for this protection is unknown; however heat stress proteins are known to influence mitochondrial ATP formation and be essential to mitochondrial protein metabolism. This study was therefore designed to determine if the protection associated with heat stress is influenced by the presence of a glycolytic (glucose) or mitochondrial (pyruvate) substrate. Rabbits were heat stressed by raising their temperature to 42°C for 15 min. Twenty four hours later their hearts were removed and papillary muscles mounted isometrically and stimulated at 1 Hz at 37°C. Control papillary muscles were prepared identically but without heat stress. Contractile recovery after 30 min of hypoxia without substrate was examined in four experimental groups and expressed as a percentage of baseline function: Group 1, control perfused with pyruvate (n = 12), recovery rates at 30, 60 and 90 mins after hypoxia were 47·1 (2·6)%, 54·8 (4·7)%, and 58·9 (5·4)% respectively; group 2, heat stressed perfused with pyruvate (n = 12). Recovery rates at 30, 60 and 90 mins after hypoxia were 60·9 (7·3)%, 75·3 (9·6)% and 84·2 (11·35)% respectively. At each time the differences between these groups was significant (p < 0·05, Wilcox signed rank). By contrast group 3, control perfused with glucose (n = 12) and group 4, heat stress perfused with glucose (n = 12), did not differ at any time and were similar to group 2 in terms of recovery. The 72 kD and 65 kD stress proteins were raised in right ventricular tissue from heat stressed groups.

These results suggest that heat stress preferentially increases mitochondrial resistance to hypoxia and reoxygenation whereas protection of glycolytic pathways seems minimal.

Preconditioning with heat stress protects the ischaemic myocardium

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Heat stress and the subsequent expression of stress proteins has been shown to offer protection to the isolated in vitro rabbit heart, although no benefit is apparent with an in vivo rabbit model. This study was designed to investigate this discrepancy and to ascertain if heating itself has any effect on the blood which could negate the protection derived from myocardial stress protein synthesis. We used an isolated blood perfused rabbit model in which a support rabbit (heat stress or control) perfused an isolated donor rabbit heart (heat stress or control). The heat stress consisted of whole body hyperthermia at 42°C for 15 minutes, 24 hours before the experiment. Donor rabbits were then anaesthetised and their hearts removed. These isolated donor hearts were then subjected to 45 minutes of regional ischaemia followed by 120 minutes of reperfusion. Infarct size was measured with triphenyl tetrazolium chloride and expressed as a percentage of the risk zone (I/R) measured with fluorescent microspheres. Results show that heat stress protects the rabbit heart in the absence of heat stressed blood (control support rabbit perfusing control isolated heart, I/R = 34·7 (3·7)% (n = 15) compared with control support rabbit perfusing heat stressed isolated heart, I/R = 23·5 (3·3)% (n = 16) p < 0·05). When the support animal has been heated, however, I/R appears greater in both groups (control isolated heart I/R = 44·9 (3·3)% (n = 12), p < 0·05 *v* control/control and heat stressed isolated heart I/R = 51·9 (7·0)% (n = 7), p < 0·01 *v* control blood/heat stressed heart). To ascertain if heat stress could limit infarct size in the absence of blood, we repeated the above experiment using isolated hearts perfused with Krebs buffer containing 2% bovine serum albumin; I/R in the control and heat stressed groups were 70·8 (4·3)% (n = 10) and 51·5 (5·7)% (n = 12) respectively, showing a significant protection in the heat stressed group (p < 0·05).

We conclude that although heat stress appears to precondition the heart by limiting infarct size, it also has adverse effects—probably on the blood—that may override any benefit associated with stress protein synthesis.

Myocardial resistance to calcium overload is enhanced by prior heat stress

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When any living cell is exposed to sublethal temperature increase a series of adaptive changes occurs that serves to protect that cell from subsequent increases in temperature. A group of proteins known as the heat stress proteins are the only proteins translated during such stress and play a pivotal role in providing this protection. In the heart a wide variety of insults other than heat stress, such as ischaemia, also result in heat stress protein synthesis. In the buffer perfused rat and rabbit heart, raised heat stress protein associates with an enhanced resistance to ischaemia and reperfusion. This resistance has been attributed to an increase in endogenous cardiac anti-oxidant activity. Our aim was to examine the effect of heat stress proteins on the calcium paradox, which is though to induce calcium overload injury similar to ischaemia and reperfusion but without oxidant stress. Rabbits were heat stressed by raising their temperature to 42°C for 15 min. Twenty four hours later hearts (n = 10), were removed and retrogradely perfused at 37°C with Tyrode's 1·3 mM Ca^{2+} for 15 min, before perfusion with no Ca^{2+} for five min, and finally abrupt reintroduction of 1·3 mM Ca^{2+}. Throughout the experiments hearts were paced via the right atrium at 180 beats per min. Paired control hearts (n = 10), sharing the same perfusate as their matched heat stressed hearts, were prepared identically but without heating. Five control and five heat stressed hearts were used for both 65 kD and 72 kD heat stress protein estimation. After reintroduction of Ca^{2+}, left ventricular developed pressure was better preserved in heat stressed *v* control hearts at five min (36·4 (5·4) *v* 20·8 (4·5) mm Hg (p = 0·02) respectively) and 10 min (38·3 (5·0) *v* 18·8 (4·1) mm Hg (p = 0·003) respectively). In addition creatine kinase release into the coronary effluent was diminished in heat stressed *v* control hearts at one min (10·6 (8·6) *v* 86·4 (33·7) units per min per gm (p = 0·01) respectively), and five min (4·9 (3·5) *v* 81·8 (39·6) units per min per gm (p = 0·03) respectively). Similar advantages were seen in the heat stressed group in terms of myoglobin release and contracture. Cardiac heat stress protein content for both 65 and 72 kD proteins was raised.

Heat stress seems able to increase cardiac stress protein content and limit myocardial injury associated with a submaximal calcium paradox. This study suggests that the myocardial protein associated with heat stress is not based solely on enhanced anti-oxidant defences.

Impaired immediate vasoconstrictor response to head-up tilt: new insights into the pathophysiology of vasovagal syncope

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Upright tilt testing in the evaluation of unexplained syncope is now accepted as a valuable diagnostic technique. The exact mechanism of neurally mediated syncope, however, and the factors leading to individual susceptibility to orthostatic stress remain obscure. Given that many clinical episodes of syncope occur after comparatively short periods of upright posture, we hypothesised that measurable abnormalities may be present soon after tilting in patients with neurally mediated syncope. The aim of the study was to examine the initial vascular responses to head up tilt in patients with syncope that remained unexplained after clinical and non-invasive evaluation. Forearm blood flow and forearm vascular resistance were measured by strain gauge plethysmography in 53 consecutive patients (mean age 45, range 11–82) with unexplained syncope undergoing tilt testing at 60° for a maximum of 40 minutes. 26 patients (group S) became syncopal (mean time to syncope 18 min, range 5 to 38) and 27 (group N) showed normal responses. Age between the groups was not different and none of the patients had significant structural heart disease, diabetes, or evidence of neuropathy. Supine and after two min of tilt there were no significant differences in heart rate or blood pressure between the groups. After five minutes of tilt the mean arterial pressure was 94 (16) mm Hg in group S and 102 (11) mm Hg in group N ($p < 0·05$). Forearm vascular resistance (in arbitrary units) was well matched between the groups at baseline (group S:36·5 (18) *v* group N:33·4 (15), NS); however, after two min of tilt mean forearm vascular resistance was 55·5 (21·5) in group S and 86·9 (45·5) in group N ($p < 0·02$), and similarly at five min group S:49·9 (18) *v* group N:78·9 (34·3) ($p < 0·01$).

Immediate forearm vasoconstrictor responses to head up tilt are reduced in patients who have neurally mediated syncope even though syncope often does not occur until substantially later. This may explain their susceptibility to postural stress.

Morphology of the cardiac conduction system in patients with dual atrioventricular modal pathways

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The anatomical substrate for atrioventricular nodal reentrant tachycardia is thought to be within the node or else is composed of pathways in the atrial transitional cell zone. Few histological studies have been reported, none with any convincing evidence of discrete pathways. In this study, seven patients underwent standard electrophysiological assessment of atrioventricular nodal function before cardiac transplantation. A tissue block was removed from each of the explanted hearts. The tissue blocks were sectioned serially and sections included the perinodal region posteriorly extending to the orifice of the coronary sinus. The sections were studied blind to the electrophysiological findings. The structure of the atrioventricular node was normal in all with minor variations within the atrioventricular system in three cases, within the penetrating bundle in one case, fibrotic origin of the right bundle branch in two cases, and tenuous origin of the left bundle branch in two cases. There was fatty infiltration of the atrial transitional cell zone in four cases. On reviewing the electrophysiological findings, 6/7 patients were found to have dual atrioventricular nodal pathways as defined by a jump of $\geqslant 50$ ms in the antegrade conduction curve with a decrement of 10 ms.

When correlated with the histological findings, no discrete anatomical substrate could be implicated for this electrophysiological phenomenon. The difference between "normal" and "variation of normal" in these cases may be too subtle to be detected by gross morphological findings.

Prevalence of dual atrioventricular nodal pathway physiology in patients without arrhythmias

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The prevalence of dual atrioventricular nodal pathway physiology is not known. It has long been assumed that it provides a substrate for reentrant tachycardias, but its clinical significance in most people is not known. Recent mapping information suggests that the slow pathway may not be sited in the node, but may form part of the nodal input from the atrium. If this is so, dual pathways should be common. Thirteen patients with end stage heart failure, but without either a history of palpitation or documented sustained arrhythmia, were studied. All underwent standard electrophysiological assessment of atrioventricular nodal function using three quadripolar electrode catheters at the time of right heart catheterisation to assess pulmonary vascular resistance. Dual atrioventricular nodal physiology was defined as a jump in the antegrade atrioventricular nodal conduction curve of < 50 ms with a decrement in A1–A2 of 10 ms. Using this standard definition, 10/13 had dual atrioventricular nodal pathways, and seven/13 had two completely discrete atrioventricular nodal curves. Retrograde conduction was present in only four patients, and conduction curves were single in all four. No patient had atrioventricular node reentrant tachycardia induced. One patient had a concealed accessory pathway, and previously unsuspected atrioventricular reciprocating tachycardia was induced.

Thus in this small series of patients without arrhythmias, dual atrioventricular nodal physiology is common, occurring in 77%. In these patients it has had no clinical significance. This pattern, commonly considered an abnormal and potentially pathological variant, may be universal, and may in fact be normal.

Radiofrequency catheter ablation for all forms of junctional reentry: a new, safe, and effective therapy for all age groups

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Junctional reentry tachycardias (JRT), in association with accessory atrioventricular pathways (AV) present at all ages, are disturbing and may be life threatening. Drugs and antitachycardia pacing offer incomplete protection and selective destruction of accessory pathways (AP) while preserving the AV node has hitherto usually required surgery. Radiofrequency (RF) energy delivered endocardially via steerable catheter electrodes usually causes painless and localised necrosis and was therefore used to treat 28 patients (15 women), mean age 33 (range 7 to 62) with refractory JRT. In 13 patients ablation was performed during their first electrophysiology study. Seventeen patients had the Wolff-Parkinson-White syndrome (12 left sided, two right sided, 2 posteroseptal, and one anteroseptal AP), four had concealed left free wall AP, five had typical AV nodal reentry tachycardia (AVNRT), one atypical AVNRT, and one patient had a Mahaim AP. In all patients, ablation of the AP was attempted and for AVNRT, ablation was directed at the slow pathway. Successful ablation of the target pathway was achieved in 22 out of 28 (78·6%) and in 17 of the last 20 (85%) procedures. Failure occurred with three left free wall AP (one concealed) and both posteroseptal AP. Recurrent atrial fibrillation (AF) prevented ablation of one typical AVNRT although one left free wall AP was successfully ablated during AF. Potentials presumed to arise from the AP were recorded in only 15 patients but were always associated with successful ablation. Other electrogram variables (AV interval, AV amplitude ratio, V-delta interval) were not always helpful in distinguishing successful from unsuccessful ablation sites. Loss of pre-excitation within four seconds of delivery of 30 W of RF energy was permanent except in one patient eventually cured by energy delivery above rather than below the mitral annulus. There was no complication related to the ablation procedures and after successful ablation all have remained asymptomatic and well over a mean follow up period of 3·6 (range one to eight) months. Intermittent asymptomatic pre-excitation has returned in one patient after right free wall AP ablation. Function of the AV node was normal in all patients at the end of the procedure although one developed right bundle branch block immediately after ablation of an anteroseptal AP.

Radiofrequency ablation appears to be a safe and effective treatment for refractory junctional reentry arrhythmias and should be considered early in their clinical course.

Relation of right ventricular isolation procedures to postoperative ventricular arrhythmias

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In patients with arrhythmogenic right ventricular disease, right ventricular isolation procedures are accepted management options for life threatening ventricular arrhythmias. The aim of this study was to compare the occurrence of ventricular arrhythmias after surgery in patients undergoing total or partial isolation procedures. Signal averaged electrocardiograms were performed in all and the presence of late potentials was related to postoperative arrhythmic events. Late potentials were defined as QRS duration exceeding 120 ms and low amplitude activity within the terminal 40 ms of the signal averaged electrocardiograms with a root mean square value of less than 40 μV. All patients had late potentials preoperatively. Nine patients who underwent a right ventricular isolation procedure were studied. Four had total right ventricular isolation and five had disconnection of part ($<40\%$) of the right ventricular free wall. There have been four postoperative ventricular arrhythmias (44%) but all patients are controlled with therapy that had previously been ineffective. Mean postoperative follow up is 29 months. Late potentials were absent after operation in three of the four patients undergoing total right ventricular isolation, and these patients have had no ventricular arrhythmias. The patient with positive late potentials experienced symptomatic runs of non-sustained ventricular tachycardia, abolished by antiarrhythmic therapy (25% arrhythmia occurrence). All five patients who had partial isolation of the right ventricle continue to have late potentials postoperatively and three have developed new ventricular arrhythmias (60%), differing in rate and morphology from their preoperative arrhythmia.

This study shows that total isolation of the right ventricle is associated with fewer postoperative ventricular arrhythmias. The development of new ventricular arrhythmias postoperatively suggests that residual late potentials are important in the genesis. Thus despite its more radical nature, total right ventricular isolation is the preferred surgical approach in patients with arrhythmogenic right ventricular disease.

Plasma fibrinogen, medical history, and prevalent coronary heart disease in the Scottish Heart Health Study

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In the Scottish Heart Health Study plasma fibrinogen was measured in 8824 men and women aged 40 to 59 as part of a cardiovascular survey. It was related to history of high blood pressure, diabetes, stroke, or parental or sibling history of heart disease. Fibrinogen was raised in each case. It was significantly raised after correction for age and smoking, except for diabetes and stroke in women. A case control analysis was carried out defining myocardial infarction and angina from medical history, chest pain questionnaire, and electrocardiogram. Plasma fibrinogen was raised in all categories of myocardial infarction and of angina, compared with controls, in both sexes. After adjustment for age, family history, smoking and drinking, body mass index, blood pressure, total and high density lipoprotein cholesterol, triglyceride, and uric acid concentrations, the odds ratios for disease were calculated across the quartiles of plasma fibrinogen. Odds ratios for myocardial infarction were higher for men than women, were significant in all quartiles of fibrinogen, and showed a significant linear trend. The same was also true for angina. In women none of the odds ratios reached statistical significance after multiple adjustment either for myocardial infarction or for angina pectoris, although some odds ratios were significantly raised when adjusted for age alone.

Incidence of stable angina pectoris in a population survey

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There are no recent data on the incidence of stable angina pectoris in the United Kingdom. The aim of this survey was to measure incidence prospectively in a selected general practice population. All 102 partners from a stratified random sample of 17 general practices in the City of Southampton were invited, and each agreed to refer all new patients presenting for the first time with suspected non-acute cardiac chest pain to a district general hospital open access chest pain clinic. From a total of 285 referrals between September 1990 and the same month in the following year, 67 (24%) had definite angina and 95 (33%) had definite or possible angina, according to established criteria. From the reported age and sex structure of the practice population of 189 062, the age and sex specific incidence rates per 1000 per year were calculated with 95% confidence intervals (95% CI): men aged $\leqslant$30: 0; 31–40: 0·44 (0·09–0·80); 41–50: 0·43 (0·05–0·81); 51–60: 1·32 (0·57–2·07); 61–70: 2·32 (1·27–3·36); and for women in the same age bands: 0; 0·08 (0–0·25); 0·56 (0·11–1·01); 1·05 (0·36–1·73), and 1·01 (0·35–1·67). For definite angina the crude incidence rate for this population was 0·42 (0·32–0·52) per 1000 per annum, and for definite and possible angina it was 0·60 (0·48–0·72). Men aged 61–70 had a fivefold higher incidence compared with the 41–50 age group.

From this random study sample it is estimated that Wessex region population will have 1104 (95% CI 841–1366) new definite angina pectoris cases annually. With prevalent disease estimated at 15 000 middle aged men (the number of women with angina is unknown) in this region current cardiological resources at district and regional level are inadequate for the investigation and treatment of angina pectoris.

A possible new non-invasive diagnostic technique confirms South West Scotland as a high risk area for coronary heart disease

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Scotland has for a long time been recognised as a high risk area for coronary heart disease with parts of Ayrshire amongst the worst affected. Early diagnosis of persons at risk would be advantageous as this would afford greater opportunity for preventative or corrective regimes to achieve success. The development of non-invasive diagnostic techniques is being particularly encouraged (EC Biomedical and Health Research Programme, 1991–4) and this paper presents data on the use of hair calcium (Ca) as a diagnostic aid for coronary heart disease. The technique was developed in Hungary where the proximal end of scalp hair has been analysed for Ca by x ray fluorescence. This has shown that populations normally exhibit a two peaked log normal distribution for hair Ca concentration. The mean concentrations for the low and high groups are significantly different ($P < 0{\cdot}001$) at 350 and 1500 mg/kg respectively. This technique has also shown that patients suffering from coronary heart disease have considerably lower hair Ca concentrations than comparable healthy controls and that these low concentrations predated admission to their hospital. Examination of hair and aorta Ca concentrations of necropsy samples showed that when hair Ca concentration was high aorta Ca concentration was low with the converse also true. High aorta Ca concentration was associated with severe alterations in the vessel wall. Samples of scalp hair were obtained from 102 apparently healthy employed male volunteers in Ayrshire and analysed for Ca. These showed a single log normal distribution about a mean of 320 mg/kg. Only one sample had a value (1420 mg/kg) comparable with those found in other studies around the higher peak of 1500 mg/kg.

Thus this Scottish population differed from earlier Hungarian and Japanese studies where the bi-modal distribution was found and from a Zambian one where only high values were recorded. It was similar to two other Hungarian studies on 138 acute myocardial infarction (MI) and 122 post MI patients although even these biased samples were not so one sided. It is apparent therefore that the Ca metabolism of this Scottish population is being uniformly influenced by some unique parameters. What these are and whether they are related to the high prevalence of coronary heart disease in this community can be speculated on but must await further confirmatory studies.

Clinical results of catheter ablation in the United Kingdom and Ireland

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Catheter ablation has achieved an important role in the treatment of refractory arrhythmias. It remains, however, a difficult technique and can be associated with serious complications. To assess the rising use of the technique, The British Pacing and Electrophysiology Group has commissioned a retrospective survey of ablation practice in the United Kingdom. Questionnaires were sent to 50 United Kingdom centres. Forty replies were received. Twenty seven centres (68%) have performed ablation procedures and a further 10 had referred patients for ablation. Fifteen centres agreed to complete an extended questionnaire with details of their clinical results, and 12 have done so to date. Number of patients and success rates using different systems are: *ablation of atrioventricular conduction;* high energy 254 (77%), low energy 67 (73%), radiofrequency 18 (78%), other 16 (56%), total 355 (75%). *Accessory pathway:* high energy 22 (23%), low energy 41 (49%), radiofrequency 84 (68%), total 147 (56%). *Ventricular tachycardia:* high energy 6 (0%), low energy 20 (30%), radiofrequency 2 (0%), total 26 (23%). *Atrial flutter:* low energy 13 (54%), radiofrequency 2 (50%), total 15 (53%). *Modification of av conduction:* high energy 7 (0%), low energy 9 (11%), radiofrequency 21 (86%), collagen 3 (67%), total 40 (53%). Although these results are in some cases disappointing, it should be noted that recent advances in catheter technology and technique have improved clinical results. The introduction of large surface area electrodes for low energy and radiofrequency ablation have increased success rates significantly using both of these energy sources. It is clear that ablation is effective for therapy of accessory pathways or atrioventricular nodal tachycardia, and in creating complete heart block, but remains unsuccessful in the treatment of ventricular tachycardia.

To prospectively assess the clinical efficacy and cost effectiveness of different techniques for ablation, 26 centres have enrolled in a detailed prospective study of ablation in the United Kingdom and Ireland.

Abnormal gap junction organisation in human myocardial ischaemia and hypertrophy

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By raising antibodies to a portion of the cardiac gap junctional protein, connexin 43, and using these antibodies in an immunohistochemical procedure in combination with laser scanning confocal microscopy, gap junctions can be localised, with a clarity not previously possible, through thick volumes of human myocardial tissue. To explore the structural basis for electromechanical dysfunction in chronic myocardial ischaemia and infarction, and myocardial hypertrophy, this technique was applied to study the organisation of gap junctions in ventricular myocardial samples obtained during cardiac surgery. Gap junctions in normal human ventricle are confined to the intercalated disks. The surface density of gap junction in normal human left ventricle is 0·00508 (0·00070) $\mu m^2/\mu m^3$ myocardial volume, and right ventricle has a similar density. The border zone of a healed myocardial infarct has a markedly disturbed gap junction organisation with label distributed longitudinally over the cell surface, facilitating possible intercellular electrical propagation in a similarly disorganised manner. In left ventricular myocardium in which there was obvious preoperative exercise ischaemia but no local infarction, and features of hypertrophy on histology, gap junction labelling appeared normally distributed but had a reduced surface density ($p < 0{\cdot}05$). The hypertrophied left ventricular myocardium from patients with aortic stenosis also had a reduced gap junction surface density ($p < 0{\cdot}05$). When the larger cell volume of these pathological tissues is taken into account a derived index of gap junctional content per cell shows a significantly reduced level only in ischaemic ventricle compared with normal ($p < 0{\cdot}05$), suggesting that the reduced surface density of gap junction is a feature of ischaemia, and not simply hypertrophy, in the ischaemic heart.

Gap junctions are a major determinant of myocardial resistivity. These disturbances of their quantity and distribution may account for the abnormalities of impulse propagation and conduction velocities that are recognised in ischaemic and hypertrophied ventricular myocardium, and may contribute to the arrhythmic tendency and mechanical inefficiency of these hearts.

Cellular morphology and basis for conduction in accessory atrioventricular pathways in the Wolff-Parkinson-White syndrome

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Ultrastructural analysis of surgically resected accessory atrioventricular pathways from patients with the Wolff-Parkinson-White syndrome was performed to determine, for the first time, the underlying cellular morphology and basis for conduction in this congenital anomaly. Gap junctions are a determinant of myocardial resistivity (and conduction velocity) and an immunohistochemical technique for identifying connexin 43, the major protein of cardiac gap junctions, by laser scanning confocal microscopy were performed in addition to standard light microscopy and thin section electron microscopy. Left sided accessory atrioventricular pathways were composed of myocardium of normal working ventricular type with a gap junction organisation characteristic of ventricular myocytes. Right sided pathways, despite normal light microscopic appearances, included strands of myocardium composed of highly abnormal myocytes characterised by: (*a*) aberrant myofilament organisation comprising prominent Z bands with a lack of A band material, (*b*) degenerated mitochondria, (*c*) intact intercalated disk ultrastructure with the usual arrangement of junctions, including gap junctions composed of connexin 43 with a distribution characteristic of ventricular myocardium.

Despite a noticeable absence of contractile apparatus these abnormal cells, which may comprise the entire pathway, have maintained the structures for efficient electrical coupling and therefore rapid conduction velocities.

Augmented cardiopulmonary baroreflex control in patients with neurally mediated syncope

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Patients with neurally mediated syncope can be identified by head up tilt testing but the causes of individual susceptibility to postural stress remain obscure. The accepted mechanism of the vasovagal reaction implicates cardiac afferent neural activity. Minor degrees of ventricular unloading, such as that produced by −10 mm Hg lower body negative pressure, result in muscle bed vasoconstriction mediated by reduction of the normal inhibitory action of cardiopulmonary afferents on central sympathetic outflow. The purpose of this study was to examine the activity of cardiopulmonary baroreceptors in patients who developed neurally mediated syncope on tilt testing. Twenty seven patients (mean age 48) referred for tilt testing for evaluation of unexplained syncope or presyncope were studied. All had structurally normal hearts and no evidence of neuropathy or diabetes. Thirteen (group S) had positive reactions (syncope or a fall in systolic pressure to below 50 mm Hg) to 40 minutes of 60° head up tilt and 15 (group N) showed no evidence of a vasovagal response. Forearm blood flow was measured by mercury in silastic strain gauge plethysmography before and after two minutes of −10 mm Hg lower body negative pressure. The groups were well matched for heart rate, blood pressure and forearm blood flow and resistance at baseline. During lower body negative pressure there were no significant changes in heart rate or blood pressure in either group. The increase in forearm vascular resistance (arbitrary units) was mean (SE) 6·4 (1·6) in group N and 17·0 (5·7) in group S ($p < 0{\cdot}05$). The percentage increase in forearm vascular resistance was 26·1 (7·0)% in the tilt negative patients and 49·8 (8·4)% in those with neurally mediated syncope ($p = 0{\cdot}06$).

The gain of inhibitory influence of cardiopulmonary receptors is augmented in patients with neurally mediated syncope. This may shed light on the cause of individual susceptibility to orthostatic stress.

Increased vascular resistance in chronic heart failure is not due to ultrastructural changes in the vasculature of skeletal muscle

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Chronic heart failure is characterised by increased systemic vascular resistance, and diminished blood flow to exercising skeletal muscle. The pathogenesis of the increased resistance is not known, and may be due to functional abnormalities or structural changes such as endothelial cell swelling. We have investigated the ultrastructure of the microvasculature. Needle biopsies of the quadriceps muscle were taken from seven men with normal left ventricular function (mean (SD) age 43 (22)). Surgical ablation of accessory pathways was being undertaken in four, and three underwent coronary artery surgery. The findings were compared with those from 10 subjects with New York Heart Association III or IV heart failure (age 44 (12); seven men). Four patients had idiopathic dilated cardiomyopathy, three ischaemic heart disease, and three chronic constrictive pericarditis. Samples were processed for ultrathin sectioning using ruthenium red as a basement membrane stain, and sections were subsequently stained with uranyl acetate and lead citrate. Electron micrographs were taken of 10 transversely cut capillaries from each specimen. The total cross sectional area and area of the endothelium was measured, and the true diameter was assessed by the short axis diameter. The basement membrane thickness was calculated from the mean of six readings around the periphery of the vessel. The short axis diameter in the two groups was not significantly different (3·37 (0·21) μm, chronic heart failure 3·56 (0·37) μm), nor was the total cross sectional area (11·64 (1·86) μm^2, chronic heart failure 13·56 (2·78) μm^2) nor was the area of the endothelium (4·90 (1·18) μm^2, chronic heart failure 6·00 (1·58) μm^2). The mean thickness of the basement membrane was marginally increased in the patients with chronic heart failure when compared with controls (0·31 (0·077) μm *v* 0·246 (0·047) μm, p = 0·05).

In subjects with severe chronic heart failure, the increased resistance in skeletal muscle vasculature is not due to ultrastructural changes in the capillaries nor to endothelial cell swelling.

Early complement and neutrophil activation is associated with failed reperfusion after streptokinase

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An accelerated inflammatory response after ischaemia and reperfusion may have a detrimental effect on myocardial perfusion and myocyte necrosis. After reperfusion early neutrophil infiltration is mediated in part by complement activation. No previous reports have shown very early complement and neutrophil activation in those that do not reperfuse. We have studied the acute inflammatory response in 17 patients with acute myocardial infarction treated with 1·5 MU streptokinase. Neutrophil activation (specific neutrophil elastase radioimmunoassay) and complement activation was measured (before streptokinase and at 20, 45, 75, and 120 min). Based upon a validated technique of ST analysis, reperfusion occurred in 12 patients. Baseline complement and elastase activities were not raised and were not temporally related to the duration of chest pain. Non-reperfusion was associated with a dramatic early rise in elastase activity at 20 min in three out of five patients (area under the curve 12 651 (n = 3) *v* 3993 (n = 12) ng min/ml, p = 0·01). These patients tended to have systolic hypotension during the streptokinase infusion (mean 88 mm Hg *v* 103 mm Hg). Plasma and serum samples showed evidence of early complement activation at 20 min (CH50 214 *v* 96 units/ml, C3P 18·2 *v* 44·3 ng/ml reperfused and non-reperfused respectively, p < 0·05). In those with reperfusion a delayed modest rise in elastase activity occurred (p < 0·001) largely after 45 min.

Neutrophil activation occurs during streptokinase infusion. Early marked activation may identify patients without reperfusion and may be the consequence of an antigen antibody reaction.

Identification of a hypervariable polymorphism within the cardiac β myosin heavy chain gene (MYH7): detection of genetic heterogeneity in families with hypertrophic cardiomyopathy

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Familial hypertrophic cardiomyopathy is an autosomal dominant disorder characterised by ventricular hypertrophy and sudden death in the young. Assignment of the disease locus to chromosome 14q11–12 was established and resulted in the identification of a candidate gene within the limited region—the cardiac β myosin heavy chain gene (MHY7). Subsequently, three mutations in exons 9, 13 and 27 (Tanigawa *et al* 1990; Rosenzweig *et al* 1991) have been detected implicating the role of this gene in the pathology. Genetic heterogeneity has been reported, although the proportion of families where the disease results from mutation within MYH7 has yet to be determined. The identification of a hypervariable intragenic marker would obviously represent an effective means for establishing heterogeneity, even within relatively small nuclear families. We report the identification of a highly informative (CA) n dinucleotide repeat polymorphism within MHY7; eight alleles have been detected to date in normal and affected populations. Genetic linkage analysis carried out in eight nuclear pedigrees has resulted in the detection of recombination events within two unrelated pedigrees, confirming the usefulness of this marker.

No obvious correlation between phenotype and genetic heterogeneity was found.

Tanigawa *et al. Cell* 1990;**62**:991–8.
Rosenzweig *et al. N Engl J Med* 1991;**325**:1753–60.

Mean platelet volume predicts restenosis after successful coronary angioplasty

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Platelets are anucleate and therefore incapable of protein synthesis. Their protein content and size is determined at the time of thrombopoeisis from megakaryocytes. Larger platelets are more active than smaller ones and contain more granules that store platelet derived growth factor. We postulated that large platelets may have more mitogenic activity. We measured prospectively the mean platelet volume with a resistive particle counter in 47 patients before they underwent single vessel coronary angioplasty. These patients had repeat cardiac catheterisation six months after the angioplasty (range 1·5–eight months) to assess the degree of restenosis at the angioplasty site. Restenosis was determined clinically as recurrent angina or a positive exercise test, or both, and a significant stenosis (defined as a post-angioplasty stenosis of <50% increasing to >50% at follow up). In the non-restenosis group (n = 23) the mean platelet volume was 8·0 (0·61) fl compared with 8·6 (0·56) fl in the restenosis group (n = 24) (p = 0·001). There was no significant difference in platelet count haemoglobin, mean corpuscular volume, or white cell count between the groups. In addition, to determine the biological significance of mean platelet volume in the restenotic process, the angiograms were analysed quantitatively by calliper measurements. The loss in minimal luminal diameter between angioplasty and follow up angiogram was calculated and found to be related to mean platelet volume (r = 0·56, p = 0·016).

Patients with high mean platelet volumes are thus more likely to develop restenosis after initially successful angioplasty. Megakaryocyte changes may predispose to restenosis.

Relation between myocardial collagen and echo amplitude

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To study the effect of myocardial collagen concentration on the ultrasonic backscatter signal from non-fibrotic myocardium, 25 patients (five women) were studied 355 to 2939 days (1009 (718), mean (SD)) after orthotopic cardiac transplantation at the time of annual cardiac catheterisation and endomyocardial biopsy. Patient ages ranged from 22 to 62 (mean 46 (SD 11)), donor ages were 14 to 47 (25 (8)), and the ischaemic time 90 to 245 minutes (151 (42)). All but four patients were treated with cyclosporine A and azathioprine. All were clinically well with no evidence of rejection. Five patients had angiographic coronary artery disease. Tissue was obtained from endomyocardial biopsies taken at cardiac catheterisation. Hydroxyproline:leucine ratios were used as an indication of total myocardial collagen concentration. Ultrasonic backscatter was assessed by regional myocardial echo amplitude and studies were performed within the 24 hours before catheterisation. There was a significant correlation between myocardial collagen concentration measured by the hydroxyproline: leucine ratio and septal end diastolic echo amplitude (r = 0·41, p = 0·04, y = 3·66x + 4·24). If the five patients with angiographically documented coronary artery disease were excluded from analysis the correlation was substantially improved (r = 0·51, p = 0·02, y = 4·19x + 3·89). These findings suggest that the collagen concentration of myocardium is responsible for about 20% of the myocardial backscatter signal in nonfibrotic hearts.

This supports clinical studies that show increases in myocardial ultrasonic backscatter in conditions where myocardial fibrosis occurs and also indicates the importance of myocardial collagen concentration in determining the ultrasonic backscatter signal in normal hearts.

Measurement of flow in internal mammary artery to coronary artery grafts by transcutaneous ultrasound

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Quantitative ultrasound assessment of proximal internal mammary artery bloodflow was performed using a 7·5 MHz mechanical sector probe with a 3 MHz offset Doppler echocardiogram in 26 patients between six weeks and 12 months after routine coronary artery grafting that included use of at least one internal mammary artery. Flow was detected in all 19 non-grafted right internal mammary arteries, in 16/26 left internal mammary artery grafts, and in 3/7 right internal mammary artery grafts. The internal diameters of grafted and non-grafted vessels were not significantly different (mean (SD) 2·3 (0·3) mm *v* 2·2 (0·2) mm). The flow pattern, however, in grafted and non-grafted vessels was entirely different. In the non-grafted internal mammary artery flow resembled that in other systemic arteries with a high peak systolic velocity (94·1 (30·8) cm/s) and 70 (7·2)% of volume flow occurring during systole. By contrast, grafted vessels showed a lower peak systolic velocity (56·7 (20·4) cm/s, p < 0·01), a higher peak diastolic velocity (47·5 (9·9) *v* 24·7 (7·0) cm/s, p < 0·01), and a much greater proportion of flow during diastole (65·5 (6·6)% *v* 30 (7·1)%, p < 0·01). Mean total flow was 34·2 (14·5) ml/min in non-grafted vessels, 44·4 (17·6) ml/min in left internal mammary artery grafts, and 35·3 (8·3) ml/min in right internal mammary artery grafts (p = NS). Individual resting flows in left internal mammary artery to left anterior descending artery grafts showed a significant positive correlation (Spearman's r = 0·746, p = 0·04) with myocardial scores calculated by the Green Lane system from preoperative cine angiograms.

Transcutaneous ultrasonography may provide a simple, non-invasive means of studying adaptation of internal mammary artery grafts as well as studying the physiology and pharmacology of coronary blood flow.

Current indications and complications of transoesophageal echocardiography in children with congenital heart disease

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Transoesophageal echocardiography was performed prospectively in a series of 318 selected infants and children with congenital heart disease, to define the safety and current indications of the technique in the primary diagnosis (n = 116), the monitoring of interventional cardiac catheterisation or surgery (n = 115), and the postoperative follow up (n = 87). Complications were encountered in six patients (1·9%). These included arrhythmias in three and signs of oesophageal bleeding in two. No death occurred. The information obtained by transoesophageal echocardiography was compared with that obtained by praecordial ultrasound studies in all patients, and was graded in one of five categories according to its relevance for patient management. Transoesophageal echocardiography studies were incorrect or misleading in 21 patients (7%). Additional morphological or haemodynamic information of value was obtained in 95 patients (30%). The transoesophageal echocardiography study had impact on patient management in 53 children (17%). Areas of improved insights in the primary diagnosis and for postoperative follow up included venous connections, two atrial septal and chamber morphology, atrioventricular valve and junction morphology, the left ventricular outflow tract, and after a Mustard or a Fontan procedure. In the perioperative period, transoesophageal echocardiography was inferior to epicardial ultrasound in the assessment of lesions involving the ventricular septum, the right ventricular outflow tract and the ventriculoatrial junction, but allowed for continuous monitoring in the early postoperative period. During interventional cardiac catheterisation transoesophageal echocardiography allowed for real time monitoring, exclusion of immediate complications, and haemodynamic evaluation.

Transoesophageal echocardiography is a semi-invasive diagnostic technique with a complication rate of 1·9%. The technique should be considered an integral part in the diagnostic and monitoring approach in children with complex congenital heart disease involving the venous return, the atrial chambers, and the atrioventricular junction. Biplane technology will enhance the value of the technique in the assessment of lesions involving the ventriculoatrial junction and the right ventricular outflow tract.

Role of the signal-averaged electrocardiogram in the prediction of serious arrhythmic events after myocardial infarction in the thrombolytic era

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The ability of three non-invasive tests and simple clinical variables to predict serious arrhythmic events (sudden death and sustained ventricular tachycardia) in the thrombolytic era was studied in 301 hospital survivors of myocardial infarction. Two hundred and five (68%) received intraventricular thrombolytic treatment. Signal-averaged electrocardiograms were performed within the first 48 hours, on day six, and at discharge. Holter electrocardiograms on day 6 and radionuclide ventriculography on day seven to 14 were carried out. Median follow up was 1·03 years. There were 13 arrhythmic events (sudden death 11, ventricular tachycardia two). A late potential on the 25 Hz highpass signal-averaged electrocardiogram at discharge was 64% (95% CI 36–92%) sensitive and 81% (76–86%) specific for arrhythmic events. High grade ventricular extrasystole on Holter electrocardiogram (10 or more ventricular premature complexes/hour, couplets or non-sustained ventricular tachycardia) had a sensitivity of only 38% (12–64%) and specificity of 74% (71–77%) for arrhythmic events. The best single test for prediction of arrhythmic events was left ventricular ejection fraction $<0·4$ with 75% (50–100%) sensitivity and 81% (76–85%) specificity. In a multifactor analysis involving both clinical variables and results of the three tests, predictors of arrhythmic events, in rank order, were digoxin treatment at discharge, late potential at discharge, absence of angina before myocardial infarction, and a history of previous myocardial infarction. With the results of the multifactor analysis, a discriminant score was computed which identified a high risk group (12% of the total population) with an event rate of 26% and a low risk group (88%) with a 0·8% event rate.

After myocardial infarction in the thrombolytic era, a combination of clinical and investigative variables, including the signal averaged electrocardiogram result, best identifies a small subgroup at high risk of arrhythmic events.

Chronotropic incompetence can be accurately assessed by analysis of the chronotropic response during early exercise

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The assessment of chronotropic incompetence at maximum exercise is often difficult because of the problems involved in finding the time at which the maximum workload is achieved despite the use of analysis of respiratory gases and estimations of blood lactate. To determine if the chronotropic response at peak exercise (normal range $>0·8x$ (220–age)) could be predicted from that attained during early submaximal exercise (normal range $>0·8x$ predicted heart rate), 65 patients with chronic heart failure (New York Heart Association II and III) underwent symptom limited exercise testing (Bruce protocol) with respiratory gas analysis. The predicted chronotropic response was calculated for each stage of submaximal exercise with Wilkoff's formula. All patients were in sinus rhythm and no patient was taking β blockers, calcium antagonists, or digoxin, or had evidence of exercise induced ischaemia. The peak respiratory quotient achieved at maximum exercise was 1·1 (0·1) (59/65 > 1·0). Chronotropic incompetence was found at maximal exercise in 8/65 patients, 10/64 at stage 1, 2/33 at stage 2, and 1/12 at stage 3. A strong association ($r = 0·8$, $p = 0·0001$) was found between the overall submaximal chronotropic response and the chronotropic response achieved at maximal exercise (specificity 87·5%, sensitivity 94·6%). Analysis of the chronotropic response achieved at stage 1 of exercise and that at maximum exercise showed a sensitivity of 87·5%, specificity 96·4%, a positive predictive value of 77·7%, and a negative predictive value of 98·2%. Only one false negative result was found in a patient who achieved a maximal chronotropic response of 80·1%.

This method enables chronotropic incompetence to be accurately assessed during the early stages of submaximal exercise and shows maximal exercise testing is not required. Furthermore this assessment takes into account the workload achieved at each stage of exercise, patient age, and the resting heart rate, and is likely to prove superior to the assessment of chronotropic incompetence at maximal exercise.

Use of magnetic resonance imaging to assess the long-term results of total correction of tetralogy of Fallot

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The purpose of this study was to assess the function and anatomy of right ventricular outflow tract, and pulmonary arteries by magnetic resonance imaging in conjunction with echocardiography in patients who had correction of tetralogy of Fallot 10 years before. Fourteen patients were studied, (eight male and six female) with an age ranging from 13 to 19 years. There were two groups; the first group (eight patients) consisted of patients who had relief of right ventricular outflow tract obstruction with Gore-tex patch, and the second group (six patients) underwent infundibular resection with or without pulmonary valvotomy, without outflow tract patch. Right ventricular dimensions were assessed using contiguous gradient echo images. In all patients the right ventricle was dilated and the average ejection fraction was 50% (6). The regurgitation fraction and gradient across the pulmonary valves were assessed by phase encoded flow mapping. The results corresponded with echocardiography. There were four peripheral pulmonary artery stenoses which were not detected by echocardiography. There were three other associated cardiac anomalies.

We found the magnetic resonance imaging allowed quantitative and anatomic insight of the heart in the long term follow up of patients who had correction of tetralogy of Fallot, thus supplementing the clinical and echocardiography evaluation.

Complexity, results, and complications of the first 1000 consecutive percutaneous transluminal coronary angioplasty (PTCA) procedures in a regional centre

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Analysis of the angioplasty database in the Wessex Cardiac Centre has been undertaken for the first 1000 consecutive angioplasty procedures (1983 to mid 1991) to find changes in procedure complexity, primary angiographic success rate, and the incidence of complications. Mean age for the series was 55·9 (range 28 to 83, SD 9·6), 808 (80·8%) patients were men, 200 patients (20%) had undergone previous coronary artery bypass grafting, and 51 (5·1%) patients had received thrombolysis before intervention. Procedural complexity increased with experience. Balloon dilatation was attempted in 1385 lesions (mean 1·4/patient, range 1 to 4), of which coronary graft angioplasty accounted for 120 lesions (8·7%). Comparing the first 500 with the second 500 patients, single vessel dilatation was undertaken in 411 and 334 patients ($p < 0·001$), multivessel dilatation in 67 and 97 patients ($p < 0·02$), and occlusions (TIMI grade 0) in 22 and 69 patients ($p < 0·001$) respectively. Overall angiographic success rate was 83·6%, complete success 77·9%, partial success (dilatation of some but not all lesions attempted) 5·7%, failure 16·4%. Significant differences occurred in the angiographic success rate in the different sub-groups varying from 84·6% for single lesion dilatation to as low as 35·6% for chronic occlusions. The angioplasty was uncomplicated in 903 (90·3%) patients, seven patients died while inpatients (early mortality 0·7%), emergency coronary artery bypass graft was required in 41 patients (4·1%), myocardial infarction occurred in 41 patients (4·1%) (Q wave 31, non-Q wave 10). In the second 500 patients there was one death (early mortality 0·2%), seven patients required emergency coronary artery bypass graft (1·4%) ($p < 0·001$ compared with the first 500 patients), and 12 patients sustained a myocardial infarct (2·4%) (Q wave 7, non-Q wave 5) ($p < 0·01$).

Thus despite an increase in procedural complexity, the incidence of complications has fallen with experience.

Platelet activation: an important side effect of contrast media of relevance to coronary angiography and intervention

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Platelet activation is central to the initiation of restenosis after coronary angioplasty. The main stimulus to platelet activation is believed to be the traumatised coronary artery wall resulting from balloon dilatation. Other stimuli, however, may be important. There is evidence that contrast media may generate thrombin when mixed with whole blood. Since thrombin is a potent stimulus of platelet activation and degranulation, a study was performed to establish the effect of contrast media on platelet activation. Ionic (Urograffin) and non-ionic (Omnipaque) contrast media were each added to equal volumes of blood from five normal volunteers and incubated for one minute. The platelets were then analysed for expression of two granule membrane antigens expressed on the platelet surface only after degranulation; namely the GMP140 antigen of the alpha granules and the GP53 antigen of the lysosomal membranes. Five μl of each sample was incubated with fluorochrome labelled anti-GMP140 and anti-GP53 and analysed in Coulter Epics II Flow Cytometer. This whole blood system does not involve the separation of the platelets and thus avoids artifactual activation during preparation. Considerable platelet degranulation occurred in the blood incubated with Omnipaque, 47·4% (8·5) (mean (SD)) expressed GP53, and 69·2% (9·6) expressed GMP140. When incubated with Urograffin, only 16·6% (8·7) expressed GP53, and 17·0% (9·4) expressed GMP140. Control samples with no contrast media but incubated under the same conditions with an equal volume of normal saline showed no activation; 0·14% (0·11) of these platelets expressed GP53, and 1·6% (0·3) GMP140. The differences seen were highly statistically significant.

These findings have important implications in the choice of contrast media used during coronary angioplasty; a situation where endothelial cell damage occurs in response to balloon inflation. Contrast induced platelet degranulation in this microenvironment could lead to further release of platelet derived growth factors, vasoactive substances, and haemostatic proteins that may influence rates of both acute occlusion and coronary restenosis.

Impaired myocardial microvascular function in patients with coronary occlusive disease after cardiac transplantation

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Coronary occlusive disease is the major long term problem after cardiac transplantation. It affects both proximal and distal coronary vessels and is therefore difficult to assess angiographically. Coronary flow reserve measurements offer a potentially improved method of monitoring this disease. Coronary flow reserve was assessed in seven patients with chest pain (controls) with normal coronary anatomy, and 60 patients between three months and 10 years (median 4·5 years) after cardiac transplant. A Doppler flow probe was inserted into the proximal left anterior descending coronary artery in each patient and a maximally vasodilating dose of intracoronary papaverine was given. Twenty five transplant patients had angiographic evidence of minor coronary occlusive disease (mean percentage stenosis diameter 23% (6%)) in a proximal coronary vessel (group 1), with 12 of these in the left anterior descending coronary artery (mean stenosis diameter 24% (8%)). The remaining 35 transplant patients had normal coronary angiograms (group 2). Coronary flow reserve was defined as the ratio of the peak flow velocity achieved to the resting blood flow velocity. Group 1 patients had an impaired coronary flow reserve (2·6 (1·1), Student's *t* test) compared with control patients (3·9 (0·4), p = 0·005), group 2 patients (3·9 (1·0), p < 0·001). No other variables were associated with a reduction in coronary flow reserve. Mean resting flow velocity was similar in all three groups (controls—7·4 cm/s (4·6), group 1—6·9 cm/s (5·9), and group 2—7·4 cm/s (4·8)). Mean peak flow velocity response to papaverine was reduced in group 1 patients (16·8 cm/s (13·5)) compared with group 2 patients (27·7 cm/s (16·4), p < 0·001), and controls (28·4 cm/s (15·4), p = 0·002). Coronary flow reserve and the peak flow response to papaverine are impaired in cardiac transplant patients with minor proximal coronary stenoses.

Disturbance of cardiac microvascular function contributes to the late morbidity and mortality found in cardiac transplant patients with coronary occlusive disease.

Fast-track coronary angioplasty in patients with chronic stable angina

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In patients with chronic stable angina pectoris coronary angioplasty is usually performed as a deferred elective procedure often requiring another hospital admission. Modern digital cardiac imaging equipment now allows high quality on the spot analysis of coronary artery lesions such that immediate decisions can be taken on the suitability for angioplasty treatment. This study compares the outcome of treatment of two groups of patients with chronic stable angina pectoris: those who were offered immediate (fast-track) coronary angioplasty after routine diagnostic coronary arteriography (group A), and those in whom coronary angioplasty was deferred because of more extensive and complex disease (group B). A total of 495 patients (673 vessels) were treated in this study, enrolled over a 29 month period. The primary success rate in group A (n = 129, mean age 57·3; vessels treated per patient 1·35) was 95·4%. There was no inpatient mortality and no referral for emergency coronary artery bypass surgery. One patient required emergency stent implantation (Palmaz-Schatz) for an occlusive dissection. In group B (n = 366, mean age 57·8, vessels treated per patient 1·36) the primary success rate was 90·9% (NS). Seven patients (1·9%) required emergency coronary artery surgery and three patients died during the procedure (0·8%). The median additional time required for angioplasty in group A was 27 minutes and this was not considered to be disruptive to other planned procedures within a diagnostic session.

Follow on coronary angioplasty after routine diagnostic coronary arteriography in selected patients with chronic stable angina is a safe procedure particularly if stent back up is available. This strategy reduces waiting list times for conary angioplasty and increases the cost efficiency of the procedure.

Should mild coronary stenoses be dilated?

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It is not clear whether mild coronary stenoses (<60%) should be dilated at the time of percutaneous transluminal coronary angioplasty to a more severe lesion. We report on 150 patients who had a mild (40–60%) coronary stenosis in a large epicardial coronary artery at the time of percutaneous transluminal coronary angioplasty to a significant (>70%) lesion in another vessel. Patients with total occlusion, previous angioplasty, or coronary grafts were excluded. One hundred and twenty six men, mean age 55 (39 to 76), and 24 women, mean age 58 (46 to 73) were studied. The primary artery dilated was the left anterior descending in 55%, the right in 27% and the circumflex in 12%. In 125 patients only the primary stenosis was dilated (group I). In 25 patients both stenoses were dilated (group II). Both groups had similar pre-angioplasty symptoms and severity of stenosis. Mean follow up is 3·5 years for group I and 3·6 years for group II. Forty three patients have relapsed (29%), 39 in group I and four in group II. In group I relapse was due solely to progression of the mild stenosis in only four patients (3%). In the other cases relapse was due to restenosis at the primary site or to a new lesion. In group II relapse was due to restenosis at the site of mild stenosis in one case only (4%) (NS).

We conclude that mild coronary stenoses should not be dilated at the time of PTCA to a more severe lesion as very few patients will go on to have symptoms from progression of the mild lesion. We disagree, however, with previous suggestions that dilating mild lesions leads to severe recurrence at the same site.

Omniflex or Magnarail for total coronary occlusions?

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Fifty patients were enrolled in a prospective randomised study to evaluate two angioplasty systems in percutaneous transluminary coronary angioplasty of total coronary occlusions. The age of occlusion could be estimated from previous angiography, a recent myocardial infarction, or a change in anginal symptoms. The mean duration of occlusion was 4·8 months (range two weeks to 10·5 months). Twenty five were initially allocated the Magnarail and 25 the Omniflex as the initial system. The protocol allowed a total of 20 minutes screening time with the initial system before crossover to the other system. The procedure was abandoned if the second system was unsuccessful after a further 20 minutes screening. The primary success for the Magnarail was 64·0% (n = 16/25) and for the Omniflex, 56% (n = 14/25) (NS). The mean screening time (SD) for successful procedures was 9·3 (14·8) min (Omniflex) and 7·6 (12·2) min (Magnarail) (NS). The additional system was employed in 12 instances of initial failure. This was successful in six instances improving the overall success rate to 72%. The Magnarail succeeded in 62·5% (n = 5/8) of Omniflex failures whereas the Omniflex succeeded in 25% of primary Magnarail failures (n = 1/4) (NS). In eight instances of failure with the primary system the operator did not proceed with the alternative system. Generally this was due to the presence of a large intimal dissection (6/8) that was induced by the Magnarail in five. The primary success for the Omniflex in left anterior descending coronary artery occlusions was 81·8% (n = 9/11) compared with 55·6% (n = 5/9) with the Magnarail ($p = 0·04$). The Magnarail was more successful in right coronary artery lesions, however; 72·7% (n = 8/11) *v* 37·5% (n = 3/8) ($p = 0·04$).

Thus both systems appear useful in angioplasty of coronary occlusions; the Magnarail for more tortuous right coronary artery lesions and the Omniflex for the straighter anterior descending coronary artery occlusions of the left.

Safety, efficacy, and patient toleration of a new inflatable device for compressing the femoral artery after cardiac angiography?

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Bleeding and haematomas are not uncommon after manual compression of the femoral artery after cardiac catheterisation. In this prospective randomised study a new pneumatic compression device (n = 30) was compared with manual compression (n = 37) by the cardiologist. Both groups were comparable for age, sex, current treatment with aspirin and warfarin, diameter of the arterial sheath, previous procedures via the same artery, procedure duration, blood pressure, and bleeding or presence of haematoma before arterial sheath removal. Patient discomfort was assessed as none 84% *v* 75%, mild 13% *v* 19%, moderate 3% *v* 3%, or severe 0 *v* 3% for the pneumatic *v* manual group respectively. The mean manual compression time was 13·1 (4·1) minutes. Bleeding after compression (5 *v* 2 patients, pneumatic *v* manual, NS) was successfully treated by reinflation or manual compression respectively. Significant haematomas (diameter > 10 cm) occurred in 3% (pneumatic) and 11% (manual) of patients (NS). None of the haematomas exceeded 20 cm in diameter. Haematoma before sheath removal was reduced in three patients by pneumatic compression.

Pneumatic femoral artery compression is at least as good as manual compression, is safe, easy to apply, and reduces staff involvement without increasing patient discomfort.

Collagen plug for femoral arterial haemostasis after cardiac catheterisation

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Femoral arterial morbidity has increased with the advent of interventional cardiology. This may be related to the time the arterial sheath is in situ, the larger catheter size, and concomitant anticoagulant treatment. Coronary stenting is associated with 10–20% incidence of femoral bleeding complications. We have investigated the efficacy and safety of immediate sealing of the puncture site using 180 mg of purified bovine collagen immediately after the procedure. At the end of the procedure the collagen was administered via a prototype applicator onto the femoral artery entry site without interruption of anticoagulant treatment. Inadvertent introduction of collagen into the arterial lumen was avoided by a colour coded blunt tip probing device designed to measure the skin to artery distance. Forty nine patients undergoing percutaneous transluminal coronary angioplasty and anticoagulated with heparin, aspirin, and dextran were compared with 21 patients undergoing diagnostic coronary arteriography on aspirin only. Femoral arterial sheaths were removed in the catheterisation laboratory when the activated clotting time was 412 (177) (mean (SD)) in the angioplasty group and normal in the angiography group. The manual compression time was 9·1 (10·2) min in the angioplasty group and 3·9 (1·2) min in the angiography group. Delayed bleeding occurred in one patient, and one patient who had undergone coronary atherectomy required surgical revision of the femoral artery due to plaque dislodgement. Ten patients had coronary stents implanted: there were local bleeding complications in one patient.

The collagen plug proved to be safe, simple to use and secured haemostasis quickly. These findings may have important implications for interventional procedures and for early mobilisation after routine catheterisation.

Complementary roles of biplane transoesophageal and precordial echocardiography in evaluating patients undergoing balloon dilatation of the mitral valve?

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To find whether transoesophageal echocardiography (TEE) would provide important new information on patients undergoing percutaneous balloon dilatation of the mitral valve, that could not be obtained by transthoracic echocardiography (TTE), 47 consecutive patients (mean age 59 (14) years) were prospectively studied by both TTE (n=47) and TEE (n=44, 33 biplane, 11 single plane) immediately before balloon dilatation and 24 hours afterwards. Mitral valve leaflet morphology, the subvalvar apparatus, mitral regurgitation, and the presence of atrial thrombus were specifically examined. Excellent images were provided by TEE in all patients whereas five patients could not be imaged satisfactorily by TTE. In echogenic patients mitral leaflet thickness, calcification, mobility, and the subvalvar structures could be assessed equally well by both techniques but evaluation of valve orifice and commissures was better achieved by parasternal short axis imaging. Transgastric long axis TEE views (potentially the optimal TEE imaging plane for mitral valve leaflet and sub-valve morphology) could be obtained in only 20/47 patients. Atrial thrombus was diagnosed in eight patients by TEE, and was localised to the appendage in two, and to the main cavity in six; in only one case, (a large thrombus), was this detected precordially. Whereas thrombus identification was possible using either the transverse or longitudinal plane, accurate localisation of thrombus to outside the appendage required longitudinal imaging; the anterior and superior atrial wall was involved in four patients and the posterior wall in one patient. The sixth patient had only a single plane TEE study. Valvotomy was cancelled in three of the eight patients on the basis of the TEE thrombus identification. Before balloon dilatation, TEE and TTE assessments on mitral regurgitation were concordant but after dilatation TEE was superior at evaluating patients with severe mitral regurgitation (n=3). Colour flow mitral regurgitation jets were not seen precordially in 2/3 patients whereas TEE identified both the jets and the actual leaflet tears in 2/3 patients examined.

Thus, TEE seems essential for all patients for whom balloon dilatation of the mitral valve is planned because of its superior ability to detect atrial thrombus, compared with TTE. In echogenic patients, mitral morphology, especially the orifice and the commissures, are better assessed from the precordium. After dilatation, the main value of TEE lies in assessing complications, in particular severe mitral regurgitation and its underlying aetiology.

Long-term outcome of the pulmonary autograft operation for aortic valve disease

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Between 1967 and 1984, 149 patients aged 11 to 56 (mean 33) had a pulmonary autograft operation for aortic valve disease at the National Heart Hospital, London. The pulmonary valve was replaced by an aortic homograft in 131 and with other valves (fascia lata, xenografts, and pericardial tubes) in the rest. Eighteen operative deaths (within the first three months) occurred, all before 1973. There were 35 late deaths due to pulmonary autograft regurgitation (four), myocardial failure with intact valves (seven), sudden (seven), reoperation (eight) and other (six). Pulmonary autograft regurgitation was serious in 28 (21%), requiring reoperation in 24. It was due to technical (operative) malposition in 18, endocarditis in four on previously trivial regurgitation, one dehiscence from the only strut and another "rheumatic." No obstruction or degenerative cusps change was identified. Trivial pulmonary autograft regurgitation was noted from the first year in 36 (27%) and developed after three to 13 years in a further 10. On the right side all fascia lata valves failed and 12 homografts were replaced one to 17 years later. The high incidence of sudden deaths may be attributable to poor techniques of myocardial preservation in the early days. The cumulative survival proportion for hospital survivors at 10 years is 88% (9·6) (n = 84) and 57% (20) (n = 12) at 20 years. The event free proportion in those with homografts is 69% at 10 years and 45% at 20 years. The event free proportion for endocarditis at 20 years was 87% (12).

There has been no calcification, stenosis, or cusp degeneration, nor associated haemolysis or emboli. Technical problems with the placing of the autograft and length of operation were overcome after the first 50 cases. Despite the complexity of the surgery and 10% failure of the right sided homograft in 15 years, the pulmonary autograft offers an excellent and durable aortic valve replacement for young patients and appears to have the capacity to remain little changed or unchanged by the passage of time.

Echocardiographic restenosis after successful balloon dilatation of the mitral valve?

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Follow up echocardiography was reviewed in 32 patients after successful balloon dilatation of the mitral valve to assess the echocardiographic incidence of restenosis. Successful dilatation was defined as a gain in mitral valve area of >25% and a final valve area of > 1·5 cm^2, and echocardiographic restenosis was defined as a loss of >50% of the initial gain and a decrease in mitral valve area to < 1·5 cm^2. Echocardiography was performed one year after dilatation. In all patients balloon dilatation of the mitral valve was performed using the Inoue balloon. Initial dilatation resulted in a considerable increase in mitral valve area (mean (SD) 1·0 (0·3) pre *v* 1·9 (0·4) post, p < 0·001). Paired analysis indicated a significant reduction in mitral valve area at one year (1·6 (0·4), p < 0·001). Echocardiographic restenosis was present in 8/32 (25%) at one year. After dilatation mitral valve area was significantly lower in the eight patients with restenosis compared with the non-restenotic group (1·6 (0·2) *v* 2·0 (0·4), p < 0·01), whereas after dilatation end diastolic mitral valve gradient and left atrial pressure were similar in the two groups. Echocardiography before dilatation showed considerable valvar and subvalvar calcification or both in 6/8 patients with restenosis compared with 7/24 without restenosis (p = 0·03). Of the eight patients with echocardiographic restenosis four underwent mitral valve replacement, two had repeat dilatation and two were treated medically because of lack of clinical symptoms.

Mitral valve area falls significantly in the first year following balloon dilatation of the mitral valve. The echocardiographic restenosis rate one year after successful dilatation is 25%, and a proportion of these patients will have mild symptoms and may be treated conservatively. After dilatation invasive parameters fail to predict restenosis but patients with restenosis do have significantly increase valvar and subvalvar calcification and have less improvement in mitral valve area immediately after balloon dilatation of the mitral valve.

Is thromboembolic risk reduced by balloon dilatation of the mitral valve?

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Spontaneous echo contrast within the heart has been shown to be a marker of thromboembolic risk. This study was undertaken to find the echocardiographic and haemodynamic factors associated with spontaneous echo contrast in patients with severe mitral stenosis, and to assess what, if any, effect balloon dilatation of the mitral valve had on these factors. Forty seven consecutive patients (mean age 59 (14)) were studied prospectively with transthoracic and transoesophageal echocardiography both immediately before dilatation and 24 hours afterwards. Thirty five were in atrial fibrillation (AF) and 12 in sinus rhythm (SR). Echocardiographic and Doppler measurements were: left atrial volume (ellipse method), mitral valve area with both planimetry and Doppler methods, mean transmitral gradient and velocity profiles of blood flow within the left upper pulmonary vein. Haemodynamic measurements were: cardiac output (Fick) and direct mean left atrial pressure, mitral valve area (Gorlin), and transmitral gradient. Spontaneous echo contrast in the left atrium was detected by transoesophageal echocardiography only. It was found in all patients in AF but in only two patients in SR. Eight patients, all in AF, had atrial thrombus. Univariate analysis showed AF ($p < 0{\cdot}001$), age ($p = 0{\cdot}003$), left atrial volume ($p = 0{\cdot}005$), and peak systolic pulmonary vein flow velocity (PSPVFV) ($p = 0{\cdot}008$) to be predictors of spontaneous echo contrast. There was no significant association with cardiac output, mitral valve area, transmitral gradient, or mean left atrial pressure. Thus patients with spontaneous echo contrast beside being in AF, were older, had larger atrial volume, and had lower PSPVFV, than those without. Multiple regression analysis showed AF to be an independent predictor of spontaneous echo contrast. Thirty nine patients were suitable for and underwent balloon dilatation of the mitral valve. Mean cardiac output, Gorlin mitral valve area, and PSPVFV increased by 24% ($p < 0{\cdot}001$), 92% ($p < 0{\cdot}001$), and 11% (NS) respectively. Mean left atrial volume decreased by 16% ($p = 0{\cdot}001$). Spontaneous echo contrast remained unchanged in all patients except three (one in SR and two in AF) in whom the intensity apparently diminished.

Thus AF is the single most powerful determinant of spontaneous echo contrast in patients with mitral stenosis and dilatation has no immediate effect on spontaneous echo contrast in almost all patients. Thromboembolic risk therefore appears to be unaltered by balloon dilatation of the mitral valve.

The incidence and prognosis of congenital aortic valve stenosis during childhood and into early adult life

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Congenital aortic valve stenosis occurred in 239 patients (155 male, 84 female) born in the Merseyside area between 1960 and 1990, giving an incidence of 4·5 per 10 000 live births. The median age at presentation was 16 months (range 0 to 20 years). Stenosis was mild at presentation in 77% of patients, moderate in 13·8%, and critical in 9·2%. Two hundred and thirty two of the 239 patients were traced. The median duration of follow up was 9·2 years (range 1 to 28 years). Sixty patients underwent 81 operations for aortic stenosis with a reoperation rate of 30·2%; 17 operations were for aortic valve replacement. Aortic regurgitation occurred in 55 of the surviving patients, a further nine operations were performed for severe aortic regurgitation. There were no sudden deaths. The mortality for the whole group was 16·7%. Actuarial and hazard analysis showed that only 5% of patients who presented with moderate aortic stenosis were free of significant events (operation, balloon dilatation of the valve, endocarditis, or death) after 20 years of follow up, compared with 69% of those who presented with mild stenosis.

An accurate assessment of the severity of aortic valve stenosis at presentation provides a reliable guide to the prognosis into early adult life.

Pulmonary autograft in aortic position (Ross operation): an initial experience

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The use of pulmonary autograft in aortic valve replacement is now in its third decade and is gaining wider acceptance as the problems of prosthetic valves become manifest. These are the initial results of the Ross operation from January 1990 to December 1991 in 17 patients with aortic valve disease. All 17 patients had aortic regurgitation except one who had severe stenosis. There was associated endocarditis with aortic root abscess in three patients, one of them was a child of 18 months with fungal endocarditis from congenital immune deficiency. The right ventricular pulmonary artery continuity was reestablished with a cryo preserved aortic homograft in one, cryo preserved pulmonary homograft in 12, antibiotic preserved fresh pulmonary homograft in two, synthetic valved conduit in one, and by direct connection in one. Associated procedures were relief of supravalvar aortic stenosis using pulmonary autograft in one and mitral valve repair in two patients. There was no mortality. All 17 patients are either in New York Heart Association grade II or asymptomatic. In this short follow up period there have been no valve failures, thromboembolic episodes, or infective endocarditis. Echocardiographic follow up shows 1+ aortic regurgitation in all patients, the systolic gradients ranged from four to 36 mm of mercury with a mean of 12.

The limitation of homograft supply to reestablish right ventricle to pulmonary artery continuity restricts this time proven procedure that would otherwise find greater usage.

Echocardiographic and clinical features are inadequate guides to the management of patients with the Marfan syndrome

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Acute aortic dissection accounts for a high mortality at a young age in the Marfan syndrome. Common practice is to undertake elective surgery in those patients whose aortic root diameter exceeds 5·0 cm. The objective was to ascertain whether clinical and echocardiographic data discriminate between patients with Marfan syndrome at high and low risk of aortic dissection sufficiently well to determine who should undergo elective aortic surgery. One hundred and forty eight patients satisfied the international diagnostic criteria for Marfan syndrome; the results of detailed physical examination and echocardiographic measurement of aortic root diameter were available for 113 people. Patients were categorised in terms of cardiac outcome into four groups: (1) well (n = 95); (2) acute aortic dissection (n = 11); (3) elective aortic valve or root surgery (n = 5); (4) death from other causes (n = 2). Comparisons were made between groups 1 and 2, as the untreated outcome in groups 3 and 4 is unknown. Figures are given as absolute numbers or as mean (SD). No significant difference between the two groups was detected in age (32·9 (13·1) *v* 37·2 (12·3) years), sex (51:44 *v* 7:4 males:females), or height (181·4 (9·3) *v* 188·3 (10·1) cm). The aortic root diameter at latest examination was significantly higher in group 2 (5·1 (1·3) cm *v* 3·7 (0·9) cm, p < 0·005). The degree of overlap in aortic root diameter, however, between the two groups was such that no value distinguishes a group of patients at high risk of dissection with sufficient sensitivity and specificity to be the sole determinant for elective surgery, with its attendant risks. The aortic root diameter exceeded 5·0 cm in only half of group 2, but a lower cutoff value would involve operating on a large proportion of patients in group 1. In three cases, furthermore, where echocardiography had been performed both before, and at the time of dissection there was no significant increase in aortic root diameter between the two measurements.

The risk of aortic dissection is higher in those patients with an increased aortic root diameter. Clinical features and aortic root diameter alone, however, are inadequate to determine who should undergo elective surgery, and acute dissection may occur in the absence of a rising aortic root diameter.

In vivo detection of endothelial dysfunction in the pulmonary circulation of children with congenital heart disease

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Endothelial function has a key role in the control of vascular tone and reactivity. To investigate whether endothelial dysfunction occurs early in children at risk of pulmonary vascular disease (PVD), we studied the response of the pulmonary circulation to graded infusions of acetylcholine (ACh, an endothelial dependent dilator) and to nitroprusside (NP, a dilator not dependent on endothelial function) in 26 children aged three to 16 years. Nine had normal pulmonary haemodynamics (controls), eight had established PVD, seven had left to right shunts resulting in increased pulmonary flow (Qp) with normal pulmonary pressure (Pp) and two had unrestrictive ventricular septal defects with increased Qp and Pp but normal pulmonary resistance (Rp). Intra-arterial flow velocity was measured in a lower lobe segmental vessel using a Doppler catheter, and vessel diameter was measured by quantitative angiography. In the controls, there was a dose dependent increase in flow velocity in response to ACh (97 (7)% after 10^{-6} mol/l ACh), and an increase of 53 (10)% in response to NP. By contrast, in patients with PVD the response of flow velocity to ACh (33 (7)%, p < 0·01) and to NP (7 (23)%, p < 0·01) were both impaired. In the patients with increased Qp and normal Pp there was an impaired response to ACh (49 (8)%, p < 0·01), but response to NP was preserved (43 (9)%, p > 0·20), indicating endothelial dysfunction. The two subjects with increased Qp and Pp but normal Rp had impaired responses to ACh and NP. Arterial diameter was unchanged during ACh infusion in all subjects, and only increased modestly in response to NP (⩽10%), indicating that the major site of action of both agents is distal to the segmental pulmonary arteries.

Endothelium dependent pulmonary artery relaxation in vivo is impaired in young patients with increased pulmonary flow secondary to congenital heart disease, even in the presence of normal pulmonary resistance. Such impairment may be an important early event in the pathogenesis of pulmonary vascular disease.

Regulation of coronary artery tone by nitric oxide in humans: different role in epicardial and resistive vessels

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Eleven patients (mean age 47, range 28 to 61, seven women) with normal epicardial coronary arteries were studied. All medication was discontinued >48 hours before the study. Femoral artery blood pressure (BP) and the surface electrocardiogram were monitored continuously. Coronary artery diameter was measured using quantitative angiography. Coronary sinus oxygen saturation (CSO$_2$) was measured continuously using a fibreoptic catheter in seven patients. All infusions were given intracoronary at 2 ml/min via the diagnostic angiography catheter. In the first two patients studied, N^G-monomethyl-L-arginine (LNMMA), a specific inhibitor of nitric oxide synthesis, was given in low doses (0·1 to 5·0 μmol/min) into the right coronary artery, and no change in vessel diameter was found. Neither patient developed clinical nor electrocardiographic evidence of ischaemia. These two patients were not included in the final analysis. In the subsequent nine patients, LNMMA was infused at higher doses (4, 10, and 25 μmol/min, each for 5 min) into the left coronary artery. In five patients, incremental doses of acetylcholine (ACh) were infused (1, 10, and 100 nmol/min, each for 3 min) before and after the LNMMA infusion. Finally, in all patients, sodium nitroprusside was infused to reverse the effects of LNMMA. No patient developed myocardial ischaemia. The heart rate and BP remained unchanged. LNMMA, compared with the control saline infusion, caused a concentration dependent fall in CSO$_2$ from mean (SD) 39(8) to 35(8)% (p = 0·035) at 25 μmol/min LNMMA, and a reduction in distal left anterior descending coronary artery (LAD) diameter from 1·68 (0·26) to 1·58 (0·20) mm (p = 0·035) at 25 μmol/min LNMMA. Proximal LAD diameter remained unchanged, 3·10 (0·62) *v* 3·05 (0·63) mm (p = NS). ACh, compared with the control saline infusion, caused concentration dependent dilatation of distal and proximal LAD before (distal: 1·98 (0·33) *v* 1·63 (0·20) mm, p = 0·04; proximal: 2·93 (0·62) *v* 2·51 (0·42) mm, p = 0·035, ACh 100 nmol/min *v* control respectively) but not after (distal: 1·65 (0·37) *v* 1·63 (0·20) mm; proximal: 2·51 (0·57) *v* 2·51 (0·42) mm, both p = NS, ACh 100 nmol/min *v* control respectively) the LNMMA infusion. ACh caused a concentration dependent increase in CSO$_2$ both before the LNMMA infusion (60 (7) *v* 38 (8)% at 100 nmol/min, p = 0·0007) and after (57 (15)%, p = 0·011 compared with control, p = NS compared with ACh before the LNMMA infusion).

Inhibition of nitric oxide synthesis in the human coronary circulation caused a decrease in basal distal LAD diameter and basal coronary blood flow assessed by CSO$_2$. Epicardial coronary artery dilatation in response to ACh is nitric oxide-dependent, but coronary resistive vessel dilatation is not.

Non-invasive detection of endothelial dysfunction in systemic arteries of children and adults at risk of atherosclerosis

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Endothelial dysfunction is an early event in atherogenesis and has been shown invasively in adults with established atherosclerosis. We have used high resolution ultrasound to study endothelial function in presymptomatic children and adults at risk of vascular disease. Superficial femoral artery (SFA) diameter and brachial artery (BA) diameter were measured at rest, during reactive hyperaemia (increased flow causing endothelium dependent dilatation), and after sublingual nitroglycerine (GTN, dilatation independent of endothelial function) in 100 patients; 50 controls aged eight to 57 (30 SFA, 20 BA), 20 smokers aged 30 to 52 (10 SFA, 10 BA), 10 children with hypercholesterolaemia aged eight to 16 (SFA) and 20 adults with coronary artery disease aged 54 to 67 (10 SFA, 10 BA). Blood flow velocity was measured at rest and during hyperaemia using Doppler. Images of sufficient quality for analysis were obtained in 94 cases (94%). In controls, there was an inverse relation between vessel diameter and flow mediated dilatation ($r = -0·81$, $p < 0·001$). In arteries $\leqslant$6 mm diameter, dilatation was 10 (2)%. By contrast, in smokers and children with hypercholesterolaemia, flow mediated dilatation was considerably reduced (SFA in hypercholesterolaemic children 0 (1)%, SFA in smokers 0 (1)%, BA in smokers 4 (2)%, all $p < 0·01$). Flow mediated dilatation was absent in 18 subjects with known coronary artery disease (0 (1)%, $p < 0·01$) (SFA eight, BA 10). Arterial dilatation to GTN was present in all groups (12 (1)%). The degree of reactive hyperaemia was comparable in all groups (350 to 800%), and results were reproducible in repeat studies performed in 21 subjects.

Endothelial dysfunction can thus be shown non-invasively in systemic arteries of young children and adults with risk factors for vascular disease, such as smoking and hypercholesterolaemia, before anatomical evidence of atherosclerosis. Serial study of vascular physiology will permit assessment of the impact of risk factor modification at an early stage of the disease process.

Coronary flow reserve is not impaired in syndrome X

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Several studies have reported a reduced coronary flow reserve in patients with chest pain, a positive exercise test, and angiographically normal coronary arteries (syndrome X). Different methods are available to measure coronary flow reserve, but dipyridamole has consistently been the stimulus for eliciting coronary vasodilatation. We have evaluated coronary flow reserve in 19 patients by intracoronary papaverine, a well-established drug for this purpose. Epicardial coronary blood velocity was measured with an intracoronary Doppler flow probe and coronary artery diameter was determined by quantitative angiography. Estimates of coronary blood flow were made before and after intracoronary bolus injections of 8 mg papaverine in eight syndrome X patients and nine controls. The control group comprised patients with normal resting and exercise electrocardiograms and angiographically normal epicardial coronary arteries. No patient had features suggestive of hypertension, diabetes mellitus, left ventricular hypertrophy or cardiomyopathy. Coronary flow (the product of mean velocity and vessel area) was found before papaverine injection and at peak velocity change after injection. Coronary flow reserve (peak flow:baseline flow) was 3·97 (0·63) (mean (SEM) in syndrome and 4·05 (0·42) in control patients, ($p = 0·91$). With papaverine as the vasodilator agent coronary flow reserve is not impaired, in contrast to reports of reduced coronary flow reserve in syndrome X using dipyridamole.

Thus some of the manifestations of syndrome X may be due to an abnormality of the adenosine receptor.

Progressive intimal thickening after balloon angioplasty is related to rupture of the internal elastic lamina

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Intimal thickening, resulting from migration of smooth muscle cells from the tunica media and their proliferation, underlies the development of restenosis after balloon angioplasty. In this study we investigated the relation between the severity of the initial arterial injury and the extent of the subsequent intimal growth. Bilateral carotid angioplasty (five inflations; six atmospheres; 30 s duration; 60 s intervals) was performed in 12 pigs and the arteries were excised seven, 14, or 21 days (each, n = 8) later. After fixation, histological sections (n = 6) were taken at 0·5 cm intervals within the site of angioplasty and were stained with Van Giesen stain. The intimal area was measured by computerised planimetry. The depth of arterial injury in individual sections from each artery was defined as either deep (a tear through the internal elastic lamina into the media) or superficial (intact elastic lamina). The intimal area was comparable in sections showing either deep or superficial injury at seven days—(mean (SEM)) 0·223 (0·031) mm^2 *v* 0·113 (0·003) mm^2 respectively (NS), but was significantly greater in sections showing deep injury at both 14 days—0·385 (0·108) mm^2 *v* 0·110 (0·013) mm^2 ($p < 0·005$) and at 21 days—0·645 (0·083) mm^2 *v* 0·086 (0·020) mm^2 ($p = 0·0001$). Thus intimal area increased progressively with time in the presence of deep arterial injury (ANOVA $p < 0·005$), but was unchanged between seven and 21 days after superficial injury.

These results indicate that progressive intimal thickening after angioplasty occurs only when the internal elastic lamina is ruptured and suggest that the presence of an intact internal elastic lamina serves as a barrier to smooth muscle cell migration from the tunica media after balloon angioplasty.

Coronary endothelial and non-endothelial microvascular function are impaired in cardiac transplant patients early after operation

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Coronary occlusive disease after cardiac transplantation may be caused by perioperative factors damaging endothelial and vascular smooth muscle components of the coronary vasculature. Coronary flow measurements allow investigation of the vasodilatory responses of these elements of the coronary vascular bed. We investigated the hypothesis that coronary flow responses to papaverine (non-endothelial dependent vasodilator) and acetylcholine (endothelial dependent vasodilator) are impaired soon after cardiac transplantation. Fifteen transplant patients were studied three months after transplantation (group 1) and compared with 27 patients (group 2) without coronary occlusive disease on angiography (median four years after operation, range 2 to 8 years). A Doppler flow probe was inserted into the proximal left anterior descending coronary artery and incremental doses of intracoronary papaverine, and glyceryltrinitrate followed by acetylcholine were given until maximum hyperaemia was achieved. Coronary flow response was defined as the ratio of resting to peak coronary blood velocity. Coronary anatomy was assessed using quantitative coronary angiography. Coronary flow response to acetylcholine was lower in group 1 patients compared with group 2 patients—(mean (SD) 1·7 (0·8) *v* 2·7 (0·9), p = 0·003, Student's *t* test). Coronary flow response to papaverine was impaired in group 1 patients compared with group 2—3·2 (1·0) *v* 3·9 (1·0) (p = 0·04). Adjusting for the effect on endothelial dependent flow from non-endothelial dependent dilatation, there was a reduction in group 1 patients compared with group 2, but this did not reach conventional levels of statistical significance (coronary flow response to acetylcholine and papaverine was 58 (26)% *v* 70 (16)%, p = 0·09). No significant difference occurred in arterial diameter between groups after the vasodilatory drugs.

Impairment of endothelial and non-endothelial dependent microvascular vasodilation occurs soon after cardiac transplantation. This may contribute to the high early mortality in cardiac transplant recipients and may be related to the subsequent development of coronary occlusive disease.

Long-term outcome of adults with secundum atrial septal defect with and without surgical closure

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Eighty two patients with uncomplicated secundum atrial septal defect diagnosed in adult life (age 25 to 54, median 37) from 1955 onwards, were studied retrospectively. The aim of the study was to compare long-term outcome of patients who were operated on by surgical closure, with those who were not. Forty eight patients (age 26 to 51, median 36) had undergone surgical closure whereas thirty four (age 25 to 54, median 38) did not. Mean Q_p/Q_s shunt ratios were 2·5:1 for those who were operated on compared with 2·4:1 for those who were not (NS) and mean pulmonary artery pressures were 30 (8) mm Hg and 26 (10) mm Hg in the surgical and medical groups respectively (NS). All patients were reviewed between March 1989 and February 1991. There were two cardiovascular deaths in those who were operated on and one in those who were not. After a mean follow up of 25 years from diagnosis, there was no difference in patient survival in between the two groups. New atrial fibrillation developed in 16 (33%) in the operated group and 12 (35%) in the non-operated group, making a total prevalence of 28 (58%) in those who had surgery, and 19 (56%) in those who did not. Neither the incidence nor the prevalence of atrial fibrillation was different between the two groups at the follow up. Need for diuretics was also similar in both the groups, 28 (58%) needed diuretics who had surgical closure and 15 (44%) who did not. In all patients who did not have surgical closure there was no clinical, radiological, and echocardiographic evidence of pulmonary arterial hypertension at the last follow up.

We conclude that surgical closure of secundum atrial septal defects in adults is not superior to medical management. Routine surgical closure of atrial septal defects in adults offers no advantage and is not justified.

Three and a half year review of paediatric heart and heart and lung transplantation

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From 176 patients assessed for transplantation between June 1988 and December 1991, 28 orthotopic heart transplants (3 weeks to 18 years, mean 11·0) and 23 heart and lung transplants (3 to 18 years, mean 11·4) were performed. The underlying diagnosis in the heart transplant group was cardiomyopathy (n = 13 (two were anthracycline induced)) and congenital heart disease (n = 15 including two with hypoplastic left heart syndrome). The heart and lung transplant group comprised cystic fibrosis (n = 19), Eisenmenger Syndrome (n = 3), and graft *v* host disease (n = 1). Donor selection was on ABO compatibility and body size with additional Cytomegalic antibody state matching in the heart and lung transplant group. Cyclosporine, azathioprine, and prednisone were used as immunosuppressive agents with delayed onset of steroids in the heart and lung transplant group. Antilymphocytic or thymocytic globulin and methyl prednisolone is used perioperatively. In the heart transplant group 20 patients survive all with an excellent quality of life, 3 to 36 months, mean 12; actuarial survival 69% at one and three years. All deaths occurred in the first two months, five from right ventricular failure within the first week. In the heart and lung transplant group 17 patients survive 2 to 42 months, mean 16·2; actuarial survival 74% at one year, and 65% at three years. Four of the deaths have been from obliterative bronchiolitis and three further patients have significant reduction in lung function from this disease. Fourteen patients currently have a good quality of life.

Can the transplanted heart grow in children? An investigation of insulin-like growth factor gene expression

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It is fundamental for the success of the worldwide paediatric cardiac transplantation programme that the transplanted heart can grow. Therefore we have investigated expression of insulin like growth factor 1 (IGF–I), a major mediator of growth, in right ventricular endomyocardial biopsy specimens from 14 children (age range 10 to 19 years, median 15, donor age 6 to 41 years, median 19), and 10 adult recipients (48 to 59 years, median 53). Extracted ribonucleic acid (RNA) was hybridised to an IGF–I c deoxyribonucleic acid using slot and northern blot analysis. A mRNA transcript of 4 kilobases was present in the paediatric population but was absent in the 10 adults. Using radioimmunoassay, IGF–I was detected in all specimens (100 (46) pg/mg soluble protein, in the paediatric group and 16 (8) pg/mg soluble protein in the adult group), concentrations were significantly higher ($p < 0{\cdot}001$) in the paediatric patients in whom there was also a correlation with densitometric readings of slot blot autoradiograms for IGF–I mRNA ($p < 0{\cdot}001$ $r = 0{\cdot}7$). Plasma IGF–I concentrations were within expected normal ranges in all patients, mean 164 (9) ng/ml and 176 (17) ng/ml for the paediatric and adult groups respectively.

Gene expression of IGF–I mRNA in the myocardium in young transplant recipients is reassuring evidence for preservation of the molecular basis for cardiac growth.

Response to dynamic exercise after paediatric cardiac transplantation

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To assess exercise performance after paediatric heart transplantation, 18 children (11 male), surviving 0·5 to 5·4 years (mean 1·9) after transplantation underwent bicycle ergometry with a continuous graded protocol (Godfrey 1974). All were in New York Heart Association class 1. Results were compared with those from 18 age and sex matched controls (Student's *t* test). Parameters measured included: heart rate, O_2 consumption/kg, expired CO_2, minute ventilation, work rate and endurance time. Results for peak exercise are shown as mean (SD), and peak heart rate, O_2 consumption and work rate are also expressed as % of peak predicted values based on established "normal" data: Patients and controls were well matched for age (13·7 (3) years, controls 13·8 (2·2); $p > 0{\cdot}1$), and weight (48·6 (19·8), controls 58·2 (17·9); $p > 0{\cdot}1$). All other parameters differed significantly between the two groups. Patients *v* control, heart rate 145 (27) *v* 195 (12) ($p = 0{\cdot}0001$); O_2 consumption (ml/kg/min) 25·6 (6·9) *v* 41·2 (9·5) ($p = 0{\cdot}0001$); work rate (watts) 85 (41·1) *v* 181 (58·4) ($p = 0{\cdot}0001$); ventilation (l/min) 57·8 (21·9) *v* 91·5 (31·1) ($p = 0{\cdot}0017$); expired CO_2/O_2 consumption 1·23 (0·08) *v* 1·12 (0·09) ($p = 0{\cdot}0015$); endurance time (mins) 6·5 (1·9) *v* 10·7 (2·3) ($p = 0{\cdot}0001$). Per cent predicted peak values (patients *v* control) were: heart rate 70·7 (13·4) *v* 94·6 (5·6); O_2 consumption 61·6 (11·7) *v* 92·3 (16·5); and work rate 59·8 (15·1) *v* 109·6 (18). No correlation was seen between these three parameters and time from transplantation ($r = -0{\cdot}24$ to $+0{\cdot}08$; all $p > 0{\cdot}4$). Impaired exercise performance was seen in the absence of anaemia or chronic steroid usage, and in those who subjectively were of above average fitness.

Peak work rate, O_2 consumption, and heart rate are significantly reduced in asymptomatic transplanted patients and may not improve with time. Chronotropic incompetence is a likely major factor limiting exercise performance, but others, such as poor conditioning, may contribute. Longitudinal studies are required to better define those factors that limit exercise performance in this group of patients.

Pulmonary hypertensive crisis in infancy treated with extracorporeal membrane oxygenation

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Extracorporeal membrane oxygenation (ECMO) is a process of life support developed from modifications in heart lung bypass technology. It has achieved most success in the treatment of neonatal pulmonary failure but has also proved successful in the management of cardiopulmonary or cardiac failure. The ECMO service in Leicester commenced in 1988 and so far a total of 37 patients have been treated: 24 neonates, 10 paediatric patients, and three adults. From this series we present 11 infants with pulmonary hypertension treated with ECMO. Eight of these patients were neonates with persistent foetal circulation, one patient had total anomalous pulmonary venous return, one patient had functional pulmonary atresia, and one patient had a pulmonary hypertensive crisis after surgical repair of truncus arteriosus. In the absence of anatomical abnormality a survival rate of 63% was achieved in the patients with persistent foetal circulation. All the other patients presented survived. The total duration of bypass required varied from 36 to 222 hours (mean 116). All the patients with an anatomical cause for pulmonary hypertension were treated with venoarterial perfusion (cardiopulmonary support). Those with persistent foetal circulation were treated either with venoarterial or venovenous (pulmonary) support. Candidates eligible for ECMO are restricted by size and maturity (2 kg and 34 weeks completed gestation). They must not have had pre-existent intracranial haemorrhage and must have been ventilated for less than seven days. ECMO for cardiopulmonary support in cardiac patients can be used pre, peri, or postoperatively and the worldwide average survival rate is 50%. Success when used as a means to support patients who cannot be weaned from operative cardiopulmonary bypass is limited to 5%, however. Selection of patients for ECMO support is based upon the potential reversibility of the primary pathology and a failure to respond to maximal conventional medical treatment. Numerical criteria are available to assist in cases of persistent foetal circulation.

We have found this technique effective in a variety of circumstances and would advocate its use in acute pulmonary hypertension resistant to other forms of treatment.

Role of pulmonary valve insertion in reoperation for progressive late right ventricular dysfunction after repair of tetralogy of Fallot

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Clinical, echocardiographic, and radioisotope methods were used to assess the clinical outcome and right ventricular performance after pulmonary valve insertion for late right ventricular dysfunction after intracardiac repair of tetralogy of Fallot. From 1975 to 1990, 129 patients underwent successful intracardiac repair of tetralogy of Fallot. Although initially asymptomatic, 10 (7·8%) of these patients developed evidence of late right ventricular dysfunction with severe pulmonary and tricuspid insufficiency. In this subgroup, the mean age at intracardiac repair was 3·7 years and all patients had a pericardial transannular patch, extending to pulmonary branch patch angioplasty in two cases. The mean interval from intracardiac repair to reoperation was 6·2 years. No patient had a residual ventricular septal defect or right ventricular outflow tract gradient, but eight patients showed abnormalities of pulmonary arterial system (pulmonary artery branch stenosis in six, abnormal peripheral pulmonary arteries in five, systemic collateral arteries in three). Tissue valves were initially inserted in all patients with no operative deaths. Late follow up extends to 11 years (mean 7·3 years). There have been no late deaths. Three patients have required a total of four further reoperations for valve dysfunction. All achieved long term clinical improvement (New York Heart Association class I or II). Six patients underwent rest and exercise radionuclide (intravenous xenon-133) and echocardiographic study (mean 6·7 years) after pulmonary valve insertion, which confirmed preserved right ventricular function with good exercise tolerance (significant reduction of right ventricular dilatation, mean right ventricular rest ejection fraction 0·51 with >5% increase with exercise).

These results suggest that pulmonary valve insertion with transannular patch reconstruction for progressive late right ventricular dysfunction after intracardiac repair of tetralogy of Fallot can be accomplished with low operative risk and good early haemodynamic and clinical results. The progress of right ventricular dysfunction appears to be halted or at least substantially delayed by this approach although long-term review is indicated.

Determinants of myocardial revascularisation in patients with coronary artery disease: a report from the RITA coronary arteriogram register

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Steering Committee

The multicentre RITA trial coronary arteriogram register (1988–90) has been analysed to determine factors influencing the use of myocardial revascularisation procedures (coronary bypass surgery or coronary angioplasty). Of 23 968 patients with coronary artery disease 64% were referred for revascularisation, but this varied from 48% to 83% between centres. Multivariate analysis (multiple logistic regression) identified the extent of coronary disease, the number of anti-anginal drugs, catheterisation for angina, left ventricular function, and diuretic treatment (but not age or gender) as important independent determinants of revascularisation. Adjustment for these variables did not account for the between centre differences, and after multivariate analysis the odds of revascularisation at the centre with the highest intervention rate were increased by factor of 4·2, relative to the centre with the lowest intervention rate. In a separate analysis of 14 622 patients referred for a revascularisation procedure the likelihood of surgical intervention (as opposed to coronary angioplasty) was independently influenced by age, left ventricular function, the extent of coronary disease, and the participating centre. After multivariate analysis the odds of surgery at the centre with the highest surgical referral rate were increased by a factor of 5·7, relative to the centre with the lowest referral rate.

These data show important differences between centres in the use of myocardial revascularisation procedures, which could not be explained by between centre variation in their patients.

Intravenous anistreplase in acute myocardial infarction: continued reduction in mortality up to five years: long-term results of the APSAC International Mortality Study (AIMS)

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The APSAC Intervention Mortality Study (AIMS) reported a reduction in mortality maintained for one year. Long-term follow up has been continued up to 5·5 years from randomisation of the first patient. A total of 1258 of 1264 entered patients were randomised using a double blind placebo controlled design within six hours of symptoms with electrocardiographic evidence of infarction, to either 30 U intravenous anistreplase (A) or placebo (P). Heparin was introduced six hours after treatment, oral warfarin was continued for at least three months. Timolol, where appropriate, was given for up to one year. Follow up was maintained by "flagging" patients with the help of the Office of Population Census and Surveys. Data were analysed using lifetable analysis. Results are reported as odds reduction of death (OR) with 95% CI. At 30 days 6·4% of patients died after A compared with 12·1% after P (OR 50·5% (26·1–66·8%)). At one year for 624 patients in the A group, 11·2% died compared with 17·9% in the P group (OR 41·8% (19·8–57·8%)). In years 2 and 3 after therapy, estimated mortality still showed a reduction (14·3% A *v* 19·1% P (OR 29·4% (4·6–47·8%) year 2) and 15·7% A *v* 21·3% P (OR 30·8% (7·4–48·2%) year 3). In year 4, 155 A and 154 P patients were censored. Estimated mortality was 17% in A patients compared with 22·9% in P patients (OR 30·9% (8·3–47·9)%). In year 5, mortality estimates were 19·3% in A patients and 24% in P patients (OR 25·2% (1·3–43·3%)).

These results confirm that the reduction in mortality seen in the AIMS study after anistreplase in acute myocardial infarction previously reported at 30 days and one year is maintained for up to five years.

Reduced in-hospital mortality from acute myocardial infarction in the North West Thames Regional Health Authority (1980–89) with general adoption of fibrinolytic therapy

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Fibrinolytic therapy substantially reduces mortality due to acute myocardial infarction. This study assesses the impact of the introduction of this treatment on in-patient mortality during the decade 1980–89. An estimate of the number of lives saved in 1989 attributable to use of fibrinolysis was made. Figures for annual admissions and deaths due to acute myocardial infarction were obtained in the North West Thames Regional Health Authority which serves a population of 3·5 million. Between 1987 and 1990, annual usage of fibrinolytics has increased by 81%, from 1697 doses to 3066 doses. Currently fibrinolysis is given to about 50% of patients with acute myocardial infarction. During the decade, 48 861 patients, (31 868, 65% male) were admitted with acute myocardial infarction. Numbers of cases and mortality increased sharply with age. Between 1980 and 1986 mortality of acute myocardial infarction was stable at about 27%. Over the whole period however, total acute myocardial infarction mortality declined by 19% from 27% in 1980 to 21·9% in 1989 ($p < 0·0001$). Mortality fell from 6·5% to 2·6% of those aged <45 ($p < 0·0001$) (10 lives saved), 14·5% to 8·6% of those aged 45–64 ($p < 0·0001$) (89 lives saved), 29·6% to 18·4% of those aged 65–74 ($p < 0·0001$) (138 lives saved), and from 49·9% to 39·2% of those aged >74 years ($p < 0·0001$) (168 lives saved). Overall mortality in men fell by 22% from 22·6% to 17·5% ($p < 0·0001$) (248 lives saved). Overall mortality in women fell by 18% from 36·4% to 29·9% ($p < 0·0001$) (156 lives saved). Extrapolated to the national population about 5800 lives per year are being saved in England and Wales.

Increased use of fibrinolysis has resulted in important reductions in mortality especially in younger patients, and there is further scope for its use particularly in the elderly.

Results of HAL-1 (Heart Attacks in London) study: potential for earlier treatment by prehospital initiation of fibrinolytic therapy

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We investigated the potential time to be gained by prehospital treatment with fibrinolysis in London. Over a three month period London Ambulance Service crews filled in a questionnaire in cases of suspected acute myocardial infarction. One thousand two hundred forms were returned; 780 patients (65%) were men: mean age was 66 (16); 156 (13%) required immediate cardiopulmonary resuscitation. In the remainder, symptomatic data were available in 934. The major symptom was severe chest pain in 394 (42%); 257 (28%) had severe chest tightness; 158 (17%) had severe pressure in the chest. The remainder, 125 (13%) had severe dyspnoea. In 97 (10%) cases a doctor was present at the time of ambulance arrival. Exact information on time of onset of symptoms was available in 887. In these cases, 466 (52%) calls were made within the first hour from onset of symptoms, mean 21 (17) min. For this group, the mean time from onset of symptoms to the arrival of the ambulance was 31 (19) min. The mean time from ambulance arrival to arrival at hospital was 25 (10) min. The mean time from onset of symptoms to hospital arrival was 56 (22) min. In this subgroup of patients calling within one hour of the onset of symptoms, 41 (89%) were seen by an ambulance crew within an hour from the onset of symptoms whereas only 285 (61%) arrived at a hospital within this time. Recent studies have shown delays of 30 min following hospital arrival before fibrinolysis is administered.

In London, initiation of thrombolysis by trained ambulance personnel could save about 60 min in those patients calling the ambulance service within one hour of the onset of symptoms.

Thrombolytic therapy in acute infarction: circadian variations in the onset of symptoms and silent ischaemia during early recovery

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Circadian variations have an important effect on the timing of acute ischaemic syndromes and have also been shown in patients with silent ischaemia. There is, however, no information about circadian influences on the timing of silent ischaemia in the early recovery period after acute myocardial infarction although it may be an important risk factor for recurrent ischaemic events, particularly in patients treated by thrombolysis. We have recorded the time of onset of chest pain in 598 patients with acute myocardial infarction and confirmed a highly significant circadian variation peaking in the early waking hours (06.00 to 10.00 hours) with a secondary evening peak at 20.00 hours ($p < 0·01$). The circadian rhythm was independent of age, sex, smoking, hypertension, diabetes, and racial group. One hundred and forty patients, all of whom had been treated by thrombolysis, underwent 48 hour Holter ST monitoring two days later when all symptoms had resolved. Silent ischaemia was documented in 53 patients, as evidenced by either >0·2 mV ST elevation or >0·1 mV ST depression. Circadian variations in the duration of silent ischaemia were closely similar to the variations in the onset of chest pain documented in the acute phase of infarction, with morning and evening peaks at the same times.

Circadian variations in the onset of chest pain in acute myocardial infarction also have a role in the early recovery period after thrombolytic therapy, as evidenced by the timing of silent ischaemia during Holter monitoring. The data suggest that the same circadian mechanisms predisposing to coronary thrombosis in acute infarction continue to operate early after thrombolytic therapy when the patient remains at risk of recurrent ischaemic events.

Effect of late thrombolysis on left ventricular remodelling and function after myocardial infarction

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Late thrombolysis lessens mortality after acute myocardial infarction possibly by limiting left ventricular dilatation.

To examine the changes in left ventricular function and volume occurring after acute myocardial infarction, 50 consecutive patients receiving thrombolysis for a first acute myocardial infarction were studied by gated radionuclide ventriculography within 5 (3) and 56 (10) days of presentation. Left ventricular ejection fraction (LVEF) and left ventricular volume were measured; the second by a non-geometric method but without correction for attenuation. Group A ($n = 20$) and group B ($N = 30$) received thrombolysis within three hours and 4 to 24 hours of symptom onset respectively. Coronary angiography was performed at six weeks and patency of the infarct related artery (IRA) assessed. In 16/20 (80%) group A and 21/30 (70%) group B patency of the IRA was evident. Initial end diastolic volume index (EDVI) for groups A and B was similar (19·4 (6·7) ml/m^2 *v* 20·2 (7·4) ml/mm^2 NS), however, eight week EDVI for group A was smaller than for group B (20·6 (6·5) ml/m^2 *v* 27·6 (10·9) ml/m^2, $p < 0{\cdot}01$). Left ventricular dilatation (>20% increase in volume) developed in 28 patients. Amongst group A patients with a patent IRA left ventricular dilatation occurred in only 4/16 (25%); in 12/16 (75%) patients left ventricular volumes remained stable or diminished. Two out of four group A patients (50%) with an occluded IRA exhibited left ventricular dilatation; no alteration in volume was noted in the other 2/4 (50%) patients. Among group B patients with a patent IRA left ventricular dilatation occurred in 15/21 (71%) patients; in 6/21 (29%) patients left ventricular volumes did not alter; 7/9 (77%) group B patients with an occluded IRA exhibited left ventricular dilatation; in 2/9 (23%) patients left ventricular volumes remained stable. LVEF increased significantly with time only among group A patients with a patent IRA (58·7% (16·0)% *v* 66·6% (10·6)%, $p < 0{\cdot}05$).

These data indicate that early thrombolysis achieves vessel patency and limits left ventricular dilatation. Late thrombolysis, although successfully achieving vessel patency, fails to limit left ventricular dilatation after infarction. Only patients in whom reperfusion is successful early exhibit improved systolic function with time after infarction.

Temporary pacing: continuing failures in general medical management

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Temporary pacemaker insertion is a commonly performed practical procedure and has been shown to have a high associated morbidity. To assess current practice we prospectively monitored complications of temporary pacing in 40 patients referred over an eight month period from district general hospitals to a regional centre for permanent pacing. In 52·5% of cases (21/40) temporary pacemaker related complications were present and in 20% (8/40) dual problems were encountered. The indication for temporary pacing was considered spurious in 7·5% (3/40). Complete or intermittent non-capture of the ventricle was 10% of cases (4/40). The temporary pacemaker was malpositioned in 20% (8/40) of patients and in two of these was located in the pericardium, with associated diaphragmatic pacing in one case. A pneumothorax was present in 5% (2/40) cases. Eight patients (20%) had an infected temporary pacemaker on arrival at the regional centre. The mean duration of temporary pacing before transfer was increased in infected pacemakers (infected mean 8·0 days, non-infected mean 6·3 days, $p = 0{\cdot}086$), and the presence of complications was associated with an increased inpatient stay at the regional centre (uncomplicated mean 3·65 days, complicated mean 8·0 days, $p < 0{\cdot}01$). The relative experience of the 12 referring hospitals was not a factor in their individual complication rate.

Temporary cardiac pacing continues to be performed poorly and remains a cause of significant morbidity and expense. An improvement in practice will only come from improved training and supervision of junior physicians, and early transfer to a regional centre.

Chronic sensing thresholds during sinus rhythm and tachycardia: implications for pacing

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It is important that intracardiac electrograms are appropriately sensed during both sinus rhythm and tachycardia by an antitachycardia pacemaker or defibrillator so that treatment is delivered only when appropriate and not withheld during an arrhythmia. Atrial sensing thresholds during sinus rhythm and supraventricular tachycardia was measured in 28 patients with implanted pacemakers (intermedics Intertach 262-12 in 17 (group 1) and -16 in 11 (group 2)). Measurements during both sinus rhythmn and tachycardia are available in 8/17 group 1 patients and in 8/11 group 2 patients. There was no significant difference in sensing threshold during sinus rhythm and supraventricular tachycardia in either group (group 1 1·8 (0·1) *v* 1·7 (0·3), group 2 2·6 (0·3) *v* 2·3 (0·3) mV, NS). In individual patients, however, the threshold fell during supraventricular tachycardia compared with sinus rhythm in 6/16 (37%: 3 in group 1 and 3 in group 2), remained the same in six (37%: 3 in group 1 and 3 in group 2), and rose in four (25%: 2 in group 1 and 2 in group 2). The change in threshold was $\geqslant 2$ points on the available scale in 8/16 (50%). Measurements were made on more than two occasions in 10 patients. There was no significant difference in either absolute thresholds or in changes between sinus rhythm and supraventricular tachycardia.

Sensing threshold during supraventricular tachycardia cannot therefore be assumed from the sensing threshold during sinus rhythm. The threshold during tachycardia may be either higher or lower than that in the sinus rhythm. This may lead to either failure to detect tachycardia or to inappropriate sensing and pacing during sinus rhythm with induction of tachycardia.

An assessment of changes in cardiac responses to activities of daily living in pacemaker patients using a new ambulatory nuclear vest: comparison of WI and DDD pacing

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A new non-imaging ambulatory nuclear device (Capintec vest), using a single crystal probe, was used to measure changes in ejection fraction (EF) and cardiac output (CO) in six men who each had a DDD pacemaker for complete heart block. This device continuously measures changes in cardiac responses at rest and during activities of daily living such as walking and climbing stairs. Each patient underwent a conventional multigated acquisition scan to calculate resting EF. The probe was positioned over the blood pool in the left ventricle using the gamma camera and securely fastened with a plastic vest. Patients then underwent a protocol which included a 10 min corridor walk, climbing a flight of stairs, and a symptom limited exercise test (bicycle ergometer) with rest periods. The pacing mode was switched from VVI to DDD in a parallel group crossover design. The patients (age range 60–68) had been paced for six months and had normal left ventricular function (EF 50–55%). The atrioventricular delay had been individualised between 200–225 msec and upper rate response at 135–140 beats per min. Bicycle exercise duration was 10–14 min. The mean percentage change in EF and relative CO respectively from VVI to DDD were: resting mode 11% and 9%; corridor walk 13% and 12·5%; climbing stair 11% and 14%; exercise 14% and 15%.

The study suggests that this new ambulatory nuclear device can be used for assessing patients with permanent pacemakers; EF and CO are higher with DDD pacing at rest, during exercise testing, and also during activities of daily living.

Is the pacemaker syndrome caused by increased variability of pulmonary venous blood flow?

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Variation in pulmonary venous blood flow during single and dual chamber pacing was assessed using transoesophageal echocardiography and related to pacing mode preference during everyday activity. Ten patients randomly paced in VVIR, DDIR, and DDDR modes were subjectively assessed by validated questionnaires after four weeks outpatient activity. All then underwent transthoracic Doppler-echocardiography (assessing stroke volume, cardiac output, extent of tricuspid and mitral regurgitation, and bloodflow in the superior vena cava. This was followed immediately by transoesophageal echocardiography to assess pulmonary venous blood flow in VVI and DDD modes at rest and paced at 85 beats per min in a double blind crossover design. Seven patients (70%) preferred DDDR and found VVIR least acceptable with three (30%) suffering overt pacemaker syndrome and demanding early mode change, forming the (PS) group. One patient preferred VVIR and two (20%) had no preference and these formed the "tolerated VVIR" (TV) group. The remaining four patients formed the "preferred DDDR" (PD) group. Transthoracic Doppler echocardiography derived stroke volume was greater in DDD than VVI modes ($p < 0·04$) in the PS group at rest but not in either PB or TV groups (NS). Cardiac output, mitral, and tricuspid regurgitation, and variability of superior vena cava blood flow at rest and 85 beats per min in VVI and DDD modes did not differ in any group. Variability of the transoesophageal Doppler echocardiography derived pulmonary venous blood flow forward velocity integral was significantly greater, however, during VVI than DDD pacing at rest in both PS and PD groups ($p < 0·05$) but not in the TV group. Pulmonary venous blood flow reversal variability during atrial systole was significantly greater in VVI in all groups ($p < 0·01$) but did not predict mode preference.

These results suggest that left atrial receptors may be triggered by increased pulmonary venous bloodflow variability including adverse circulatory responses resulting in the pacemaker syndrome.

Beat to beat variability of stroke volume during VVI pacing as predictor of haemodynamic benefit from DDD pacing

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Asynchronous atrial contraction during VVI pacing may result in greater beat to beat variability of stroke volume compared with DDD pacing. To determine whether beat to beat variability of stroke volume during VVI pacing can predict haemodynamic benefit from DDD pacing, we undertook Doppler recordings of aortic and mitral flow during both DDD and VVI pacing in 15 pacemaker dependent patients with DDD pacemakers (mean age 49 (21), range 17–70). Heart rate was kept at 70 bpm during pacing at both modes and the atriventricular delay was set at 150 ms during DDD pacing. Left ventricular systolic function was good in all patients. Seven patients had a history of myocardial infarction and a reduced ratio of early (E) to late (A) transmitral flow velocities during DDD pacing (mean E/A 0·6 (0·2)). Eight patients had a normal E/A (mean 1·6 (0·5)). Beat to beat variability of stroke volume was defined as the standard deviation/mean value of the time velocity integral of aortic flow over 10 beats, expressed as %. Stroke volume increased by 26 (16)% from VVI to DDD ($p < 0·01$). This increase was greater in patients with reduced E/A (35 (10)% increase) compared with patients with normal E/A (16 (10)% increase; $p < 0·05$). Beat to beat variability of stroke volume was greater in VVI mode (14 (9)%) compared with DDD (4 (1)%) ($p < 0·01$). Patients with reduced E/A showed greater beat to beat variability of stroke volume during VVI pacing (20 (6)%) compared with patients with normal E/A (6(2)%) ($p < 0·01$).

Patients who derive most haemodynamic benefit from DDD pacing are those with reduced E/A and they show greater beat to beat variability in stroke volume during VVI pacing. High beat to beat variability of stroke volume during temporary VVI pacing before permanent implantation may identify patients likely to benefit from DDD mode, enabling cost effective use of modern pacemaker technology.

Long-term results of antitachycardia pacing for supraventricular tachycardia

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The long-term efficacy of antitachycardia pacing for supraventricular tachycardia is not known. Atrial fibrillation is a potential complication. The outcome has been reviewed in 101 patients with supraventricular tachycardia treated in nine centres with Intertach pacemakers. Twenty two per cent were men; mean age was 44·8 (range 16 to 84); 72 had been in hospital 3·1 (1 to 31) times with supraventricular tachycardia; 92 had unsuccessfully used four (1 to 11) drugs; 73 had atrioventricular node reentry; 23 had accessory pathways, concealed in 11, overt in 10. Complications included venous thrombosis in five, infection in five, lead displacement in two, and other problems requiring surgery in seven. During follow up of 32·4 (2 to 72) months all 101 have functioned appropriately. One patient was lost to follow up at 15 months. Ten pacemakers have been explanted (six at accessory pathway surgery, two at atrioventricular node ablation, two for infection). Two are inactive (one atrial fibrillation, one accessory pathway). Explanation rates per centre varied from 0/25 to 2/4 (0–50%). One (1%) patient has chronic atrial fibrillation (at three years), and 12% have had transient atrial fibrillation. This was not related either to age or to an accessory pathway. Six of 26 (23%) followed up for > 4 years have had atrial fibrillation, as has one of 11 (10%) followed up for > 5 years; 16% have been in hospital with supraventricular tachycardia or atrial fibrillation after implantation; 24% take antiarrhythmic drugs; and 18% β blockers.

Thus antitachycardia pacing was effective in a large series of patients with supraventricular tachycardia, particularly those with atrioventricular node reentry, reducing the need for admission to hospital and for antiarrhythmic drugs. Chronic atrial fibrillation was rare in this population.

Monocytes inhibit intimal smooth muscle proliferation: in vitro studies with human saphenous vein

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An in vitro coculture system was established to investigate the hypothesis that human monocytes and low density lipoprotein (LDL) influence the development of intimal hyperplasia in human saphenous vein. Vein segments obtained from patients undergoing coronary artery bypass surgery were opened out and 6 mm diameter discs were cut using the blade of a corneal trephine. Discs were cultured for eight days in 1·5 ml of RPMI medium containing 30% (v/v) foetal bovine serum with or without 1 mg/ml human low density lipoprotein. The medium was changed every two days and was supplemented with 1 μCi/ml of (^3H) thymidine for the last 24 hours. Monocytes were obtained 95% pure from the blood of healthy volunteers using density gradient centrifugation and 0·2–1·0 × 10^6 of freshly isolated monocytes were added to the veins on the second day of culture. Transverse paraffin sections (5 μm) were used to quantify ((*a*) monocytes stained using the monoclonal antibody HAM 56, (*b*) intimal thickness, and (*c*) (^3H) thymidine labelled (proliferating) cells. The number of monocytes/mm length detected in the intima of the veins was (mean (SE)) 0·2 (0·1), 1·5 (0·7)*, 2·2 (1·2), and 3·3 (0·7)* when 0, 0·2, 0·5, and 1·0 × 10^6 monocytes were added to the cultures ($n \geqslant 8$, *$p < 0{\cdot}05$ *v* addition of no monocytes). The corresponding intimal thicknesses were 16 (2), 12 (3), 6 (2)* and 8 (2) μm*. The corresponding numbers of (^3H) thymidine labelled cells were 5·3 (0·9), 2·6 (0·7), 2·1 (0·7)* and 2·1 (0·6)*. Adding 1 mg/ml human LDL to cultures ($n = 7$) throughout the culture period did not alter any of these values either in the presence or absence of monocytes (data not shown). The results show that monocytes migrated into the intima of human saphenous vein and inhibited intimal proliferation.

Attenuation of smooth muscle proliferation has been postulated as an underlying cause of plaque rupture, which occurs in atherosclerotic arteries in areas of highest macrophage density. Our results imply that monocytes directly inhibit smooth muscle proliferation. This in vitro model may be used further to provide an insight into the mechanisms involved.

Role of c-myc proto-oncogene expression in inhibition of vascular smooth muscle cell proliferation

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Proliferation of vascular smooth muscle cells (VSMC) contributes to angioplasty restenosis, vein graft occlusion, and atheroma formation and may be amenable to pharmacological intervention. An early response to inhibition of cellular proliferation is decreased expression of the growth-regulatory proto-oncogene c-myc. Conversely, in human atheroma VSMC proliferation, overexpression of c-myc has been described, implying that this may be part of the pathogenic mechanism. To further define the role of c-myc in inhibition of VSMC proliferation, we studied changes in c-myc expression in rat aortic VSMC during logarithmic growth in 10% serum medium and during growth arrest in response to heparin (50 μg/ml), the cyclic nucleotide analogues, 8-Br-cAMP (0·1 m/M), 8-Br-cGMP (0·1 mM), and transfer to 0·5%-serum medium. Expression of nuclear c-myc protein was localised by indirect immunofluorescence confocal microscopy and was quantified in 20 cells per condition using image analysis. C-myc RNA expression was measured by northern analysis, and proliferation by cell counting. Culture in 0·5%-serum led to a fall in c-myc oncoprotein expression from 24 (5) (SD) to 5 (1) fluorescence units at two hours ($n = 4$, $p < 0{\cdot}001$ *v* 10% serum) and inhibited proliferation from 1·6 (0·2) to 0·20 (0·04) × 10^5 cells at 48 hours ($n = 3$, $p < 0{\cdot}001$). Heparin, 8-Br-cAMP, or 8-Br-cGMP did not reduce c-myc expression at two hours (26 (2), 28 (4), 29 (3), respectively $n = 4$) or at 24 hours (not shown), despite significantly inhibiting proliferation to 0·95 (0·11), 0·77 (0·15) or 0·83 (0·12) × 10^5 cells respectively ($n = 4$, all $p < 0{\cdot}05$ *v* 10%-serum). Expression of c-myc RNA was also decreased by > 90% after two hours of 0·5%-serum culture. Flow cytometric analysis confirmed that both 0·5%-serum and the pharmacological inhibitors arrested cells in the G1 phase of the cell cycle.

The data show that reduction of serum concentration led an early decrease in expression of c-myc protein and RNA, whereas the pharmacological inhibitors did not. They therefore distinguish at least two pathways of growth inhibition of VSMC proliferation, both of which merit further investigation.

Effect of ramipril on the response to vascular injury induced by balloon catheter in the rat

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Balloon angioplasty of the coronary arteries produces endothelial denudation and disruption of the atherosclerotic plaque and damages the media of the artery. During repair of the vessel wall, medial smooth muscle cells proliferate and migrate to form fibrocellular intimal hyperplasma, which, where excessive, leads to restenosis. We examined the effect of different doses of ramipril, an angiotensin converting enzyme inhibitor that has high affinity for tissue angiotensin converting enzyme, on fibrocellular intimal hyperplasma after injury induced by balloon catheter in the carotid artery of the rat. Male Wistar rats (body weight 300–350 g) received normal drinking water (A, $n = 13$) or water containing ramipril (B, 0·1 mg/kg/day, $n = 15$; C, 1 mg/kg/day, $n = 15$; D, 10 mg/kg/day, $n = 14$) starting three days before left common carotid injury with an FG2 Fogarty balloon catheter. The animals continued to receive the drug or normal water for 14 days after the vessel injury at which time the rats were anaesthetised, exsanguinated, then perfusion fixed with 2% glutaraldehyde and 1% formaldehyde at 120 mm Hg perfusion pressure. Left and right carotid arteries were isolated and placed in fixative for a further 24 hr then embedded in araldite. Semi-thin sections were stained with toluidine blue and evaluated morphometrically using a context vision image analysis system. Results were analysed by an analysis of variance. Plasma angiotensin converting enzyme activity was reduced significantly ($p < 0{\cdot}05$) in a dose-dependent manner (A 171 (29), B 117 (18), C 100 (15), D 52 (7) U/L (mean (SEM)). A single layer of endothelial cells formed the intima of the right carotid artery. That of the injured left carotid artery was greatly thickened by smooth muscle cells and connective tissue. The cross sectional area of neointima was 0·158 (0·022) mm^2 in untreated animals (A) but was reduced at doses of ramipril > 0·1 mg/kg/day (B 0·133 (0·018) mm^2 (NS); C 0·076 (0·014] mm^2 ($p < 0{\cdot}001$); D 0·072 (0·013) mm^2 ($p < 0{\cdot}001$). These data show that ramipril reduces fibrocellular intimal hyperplasma in a dose dependent manner after balloon cather injury in the rat.

The data support the suggestion that angiotensin converting enzyme inhibition may be useful in preventing restenosis after coronary angioplasty.

Platelet adhesion after balloon angioplasty is inhibited by SIN-1 an exogenous donor of nitric oxide

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Platelet adhesion contributes to acute thrombus formation and intimal hyperplasia after balloon angioplasty. Endogenous nitric oxide (NO), endothelium-derived relaxing factor, inhibits platelet adhesion in vitro. We investigated whether SIN-1, an exogenous source of NO, inhibits platelet adhesion in vivo after bilateral carotid angioplasty in heparinised pigs. SIN-1 (intravenous; 10 μg/kg/min; $n = 6$) or placebo ($n = 6$) were given before and during the angioplasty procedure. Platelet deposition was quantified by autologous ^{111}indium labelled platelets. The depth of arterial injury, determined histologically, was defined as superficial (endothelial denudation) or sleep (rupture of the internal elastic lamina). Artery samples were taken for scanning electron microscopy. SIN-1 prolonged the bleeding time (mean (SE)) 56 (12)% *v* 4 (4)% ($p < 0{\cdot}01$) and raised platelet cyclic GMP 96 (36)% *v* 4 (14)% ($p < 0{\cdot}05$). SIN-1 significantly inhibited platelet deposition on segments with superficial injury (platelets × 10^6/cm^2) 1·92 (0·57) *v* 5·54 (0·71) ($p < 0{\cdot}005$)) and deep injury (6·66 (2·12) *v* 27·32 (7·56) ($p < 0{\cdot}05$), without affecting it on distal uninjured segments—0·18 (0·05) *v* 0·27 (0·08) ($p =$ NS). Scanning electron microscopy confirmed that SIN-1 reduced the platelet monolayer adherent to areas of endothelial denudation.

These data provide the first evidence that nitric oxide inhibits platelet adhesion in vivo. The results also indicate important therapeutic potential for SIN-1 as an agent which may influence the pathophysiological response to vessel wall injury.

Human recombinant tissue-type plasminogen activator enhances wound healing in human coronary artery endothelial cells

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Endothelial cell migration is essential to angiogenesis and the repair of breached endothelium. Tissue plasminogen activator (tPA), synthesised by endothelial cells, converts plasminogen to plasmin that disrupts the basement membrane, facilitating endothelial cell migration. Tissue plasminogen activator alone promotes migration in endothelial cells of the umbilical vein. Endothelial cells of different origins, however, exhibit functional heterogeneity. We have therefore investigated the effect of tPA on migration in a novel human coronary artery endothelial cell system. The system is serum free, permitting investigation of tPA in the absence of plasminogen. Normal coronary artery and aortic endothelial cells were isolated by collagenase digestion of surgical specimens and cultured. Confluent cells were passaged onto fibronectin coated Thermanox coverslips and characterised as endothelial by their cobblestone morphology, and granular pattern of von Willebrand factor immunoreactivity. The monolayer was wounded with a 1·4 mm resin scraper and washed in serum free medium (with 0·5% bovine serum albumin, 0·2% gelatin) to remove serum and detached cells. During 30 hours incubation in serum free medium containing human recombinant tPA (rtPA, Boehringer Ingelheim) 10–6000 IU/ml, migration was measured by sequential photography. Proliferating cells were quantified after detection by immunocytochemistry (Ki 67 antibody, Dako; specific for non-G$_0$ cells). Wound healing occurred by movement of the whole cell sheet, migration of individual cells, and cell proliferation at the wound edge. rtPA enhanced cell migration and proliferation, by a dose dependent trend, but was less effective ($p < 0{\cdot}001$) than either fetal calf serum or endothelial cell growth factor (30 μg/ml, Sigma). A combination of rtPA and fetal calf serum (supplying plasminogen) had a synergistic effect on cell migration ($p < 0{\cdot}001$). We have shown that rtPA enhances coronary artery and aortic endothelial cell migration in vitro. This effect is due to the action of tPA alone as well as to migration enhancement by plasmin. Endothelin produced during hypoxia induces endothelial release of tPA. Endogenous and administered tPA bind rapidly to endothelial cells in the presence of fibrin and resultant protection from circulating tPA inhibitors.

These results suggest that the role of tPA in coronary artery disease is not only fibrinolytic, but that it may also promote endothelial repair in the coronary artery.

White cell accumulation in infarction and its inhibition by adenosine

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White cell release products may play an important part in the extension of ischaemic damage after myocardial infarction. White cell counts are known to increase in peripheral venous samples after infarction, but whether leucocytes accumulate within the infarct zone is less clear. In an open chested pig model, myocardial infarction was produced by ligation of the left anterior descending coronary artery. Areas at risk of infarction were determined by scanning of thallium-201 injected intravenously five minutes following occlusion. White cells labelled with technetium-99m were injected intravenously into 11 pigs before infarction and in a further 11 pigs at five minutes after occlusion. Pigs were killed at 30 minutes ($n = 10$), or two hours ($n = 12$) after occlusion, and the hearts extracted, opened, and imaged on a gamma camera. Paired blocks of myocardium were taken from the infarct zone and regions of normal myocardium. Mean thallium uptake within the infarct zone was 11–23% of normal. At 30 minutes after occlusion, within the infarct area, technetium-99m labelled white cell activity was seen predominantly from accumulation of labelled cells injected before infarction (120 (24)% of activity within normal myocardium) compared to those injected post occlusion (79 (39)%). By two hours, technetium-99m white cell accumulation had increased in the infarct zone, particularly from labelled cells injected before occlusion (235 (69)% *v* 178 (93)%). This accumulation of leucocytes within the infarct was inhibited by earlier infusion of either adenosine (150 μg/kg/min; $n = 5$ or an A_2 adenosine agonist, CGS 21680 (0·25 μg/kg/min); $n = 6$ (39 (21)% and 45 (15)%).

These results showed that white cell accumulation occurs with infarcted myocardium and that this may occur by a combination of trapping and migration of white cells. This may be inhibited by adenosine, a substance known to be released by the ischaemic myocardium.

Deletion within chromosome 22q11 is an important cause of isolated heart defects and the cause of over 90% of cases of DiGeorge syndrome

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We have studied 33 children with DiGeorge syndrome (DGS) (immunodeficiency, hypocalcaemia, outflow tract heart defects, dysmorphic facial appearance). The cardiac lesion was interrupted aortic arch in 16, tetralogy of Fallot or pulmonary atresia in eight, truncus arteriosus in three, pulmonary valve stenosis in two, secundum atrial septal defect in one, an aortic coarctation with atrioventricular septal defect in one, ventricular septal defect in one, and an aberrant right subclavian artery in one. An interstitial deletion of chromosome 22q11 was visible in 9/33 on high resolution chromosome analysis. Molecular genetic analysis detected submicroscopic deletions of 22q11 in a further 22 cases. Thus we have detected 22q11 deletions in over 90% of DiGeorge syndrome cases. No other chromosomal abnormalities were found in this series. A prospective study of children referred to our regional cardiothoracic centre has identified nine cases of interrupted aortic arch over two years. Five of these developed additional features and have been included in our cytogenetic and molecular genetic study of DiGeorge syndrome. Thus half of these patients with DiGeorge syndrome had interrupted aortic arch, and more than half of a prospective series of interrupted aortic arch had DiGeorge syndrome. It is suggested that children with interrupted aortic arch should receive only irradiated blood products until T lymphocyte function has been shown to be normal in order to prevent graft versus host disease. Four families where a parent with an isolated outflow tract defect has had offspring with more severe cardiac defects, including one case of DiGeorge syndrome, have been identified. Deletions within 22q11 were identified in the affected persons in all four families.

Chromosome 22q11 deletions are an important cause of major heart defects that can recur within families.

Coarctation of the aorta: difficulties in prenatal diagnosis

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The diagnosis of coarctation of the aorta in the fetus is usually suspected when there is a disparity between the relative sizes of the left and right heart structures. These findings, however, can also be detected in some fetuses in whom there is no evidence of a coarctation postnatally, so that this diagnosis can be impossible to predict or definitively exclude in every case. Furthermore, in early pregnancy, the relative sizes of the left and right sides of the heart may appear normal despite the presence of a coarctation lesion. Over a 10 year period, the diagnosis has been correctly made in 54 fetuses, suspected but not proved in 24 and overlooked prenatally in nine. The echocardiograms of these 87 fetuses were retrospectively examined to establish diagnostic criteria for this condition in fetal life. Measurements of the ventricular widths, diameters of the great arteries, or the diameters of the atrioventricular valvar orifices, did not allow clear distinction between cases that definitely had a coarctation and those in whom the diagnosis was not proved. The appearance of the aortic arch, particularly in the horizontal projection, was more helpful in distinguishing cases of coarctation, although this was not foolproof. In cases where the arch was adequately imaged, a hypoplastic arch enabled correct diagnosis to be made in 80% of proved coarctations. The arch was of normal appearance in 75% of unproved cases and in 67% of cases overlooked prenatally. The most severe forms of coarctation are associated with relative hypoplasia of the left heart structures compared with the right and a correct diagnosis can be made in early pregnancy. The milder forms of coarctation are, however, consistent with a normal early fetal echocardiogram. In late pregnancy, it may be impossible to categorically exclude coarctation, as the right heart structures may appear larger than the left in the normal fetus after 28 weeks.

True incidence of cardiological abnormalities in Noonan syndrome: phenotypic diagnosis and echocardiographic assessment of 118 patients

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Noonan syndrome is one of the most common syndromes in paediatric cardiology practice, yet the incidence of cardiac abnormalities is unknown largely because of difficulties with: (*a*) assembling a substantial unbiased cohort, (*b*) phenotypic diagnosis, and (*c*) defining the common accompaniments—pulmonary stenosis and hypertrophy of left and right ventricles. These difficulties have been overcome by randomly selecting 145 patients from the Noonan Syndrome Society (United Kingdom), using photoanthropometric analysis by two geneticists, defining pulmonary stenosis as Doppler >3 m/s or previous intervention, and left or right ventricle hypertrophy as end diastolic thickness >2 standard deviations (SD) from normal controls ($n = 84$). Of these 145 there were 27 genetically atypical, thus 118, age range one month–41 years (mean 10·3 years) were studied. Pulmonary stenosis was present in 28 (24%) but Doppler was >2 SD from normal in 42 others. Left ventricular hypertrophy was found in 29 (25%), none of whom had pulmonary stenosis, and was severe ($>1{\cdot}7$ cm) and diffuse in five, confined to the anterior septum in 19, and a discrete subaortic shelf in five others. Severe left ventricular outflow obstruction was uncommon, range 1·4 to 4·0 m/s (mean 2·1). Hypertrophy of the right ventricle was documented in 20: 7/20 had pulmonary stenosis and eight had left ventricular hypertrophy. Other abnormalities were atrial septal defect (9%) and mitral valve prolapse (3%).

The detailed characterisation of the cardiological problems in Noonan syndrome is an aid to both phenotypic diagnosis and genetic counselling, and is a prelude to any natural history studies or gene linkage analysis. Echocardiographic assessment of all patients with the Noonan phenotype is mandatory.

Pregnancy in cyanotic congenital heart disease: maternal complications and factors influencing successful fetal outcome

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A total of 416 patients with congenital heart disease had 822 pregnancies; 45 patients who were cyanosed (operated and unoperated) had 96 pregnancies when aged 15 to 41 (mean 24). Medical terminations were excluded. Ten patients (22%) had prenatal complications from failure (eight patients) and supraventricular arrhythmias (two patients). Perinatal complications occurred in four patients (9%); bacterial endocarditis in two, with one death after late diagnosis), pulmonary embolism in one, and cerebral embolism in one. Of 96 pregnancies, 40 (42%) resulted in a live infant, two with congenital heart disease. Only 16 infants were full term with a mean weight of 2575 g. Fifty four (56%) miscarriages occurred at six weeks to five months. Two babies stillborn at eight months had congenital heart disease. The following factors were examined for their predictive relation with successful outcome: (*a*) basic anomaly in mother, divided into four groups: (A) tricuspid atresia or single ventricle, (B) pulmonary atresia or tetralogy of Fallot, (C) Ebstein's Anomaly plus atrial septal defect, (D) corrected transposition plus ventricular septal defect and pulmonary stenosis; (*b*) haemoglobin at beginning of pregnancy; (*c*) systemic arterial oxygen saturation; (*d*) age; (*e*) ability index; (*f*) previous surgical shunt. In a univariate analysis, age and presence of a shunt were not significantly associated with foetal outcome, whereas haemoglobin and arterial oxygen saturation were each strongly related ($p < 0{\cdot}0001$). From multivariate logistic regression analysis an adjusted haemoglobin value was derived in which disease group A was equivalent to an additional 2 g/dl, and the presence of a shunt was equivalent to a reduction of 1 g/dl. The resulting score was strongly associated with the risk of miscarriage. A similar rule was derived for arterial oxygen saturation, confirming that it is the lack of oxygen rather than hyperviscosity that is the cause of foetal death.

Although there is a high complication rate in the pregnant cyanotic patient, the risks to the mother and foetus may be minimised with optimal, combined informed cardiological and obstetric care.

Coronary artery anatomy in transposition of the great arteries: is diagnosis by echocardiography accurate?

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Variations in the anatomy of the coronary arteries are well recognised in complete transposition of the great arteries. The arterial switch operation is the treatment of choice and involves relocation of the coronary arteries. We wished to establish the accuracy with which echocardiography could be used to identify coronary artery anatomy. In our series, unusual coronary artery anatomy was the cause of death in 2·9% (4/138 patients). Coronary artery anatomy was assessed prospectively by cross sectional echocardiography in 53 consecutive infants with transposition of the great arteries. A Hewlett-Packard Sonos 500 and a Ving-Med 750 with a 5 MHz short focus sector scanner were used. The images were taken in a short axis high parasternal view, augmented with use of cine loop and slow motion replay, coded and recorded. Comparison was made with the findings at operation. The mean time taken to record coronary artery anatomy was 3·8 min (maximum 13 min) although repeat imaging after balloon atrial septostomy was required in five. By the classification of Yacoub *et al*, we correctly coded 42/45 of those with type A, 1/1 type B, 0/0 type C, 1/2 type D, 2/3 type E, and 1/2 that were unclassifiable. The sensitivity for identifying abnormal coronary arteries was 63% and specificity was 93%.

Echocardiography can be used to determin coronary artery anatomy in transformation of the great arteries. This may facilitate planning of the operative procedure by the surgeon.

Congenital heart disease in adults: respective roles of magnetic resonance imaging and transoesophageal echocardiography?

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Conventional diagnostic techniques are often inadequate in defining the complex anatomy and physiology in adults with congenital heart disease. This prospective study reports the diagnostic value of magnetic resonance imaging (MRI) and transoesophageal echocardiography (TOE) in 18 patients, 14 operated and four unoperated, aged 23–57 (mean 36), with tetralogy of Fallot in six, single functional ventricle in five, pulmonary hypertension in two, transposition of the great arteries in one, corrected transposition in one, aortic coarctation in one, common arterial trunk in one, and atrioventricular septal defect in one. They all had unresolved diagnostic questions remaining after a routine clinical evaluation which included transthoracic echocardiography. The MRI used a 0·5 Tesla magnet to obtain multiplane spin echo images and phase shift velocity maps; TOE used a single plane 5 MHz probe. A total of 102 predefined questions were answered by MRI and TOE, of which 54% were answered by MRI alone, 46% by TOE alone, and 76% by their results combined. Also, TOE and MRI jointly produced 14 new unexpected findings. With a simple scoring system, MRI was superior to TOE in showing pulmonary artery anatomy, extracardiac shunts and conduits, and the ventriculoarterial connexion. Velocity maps were important in quantifying stenoses of extracardiac conduits; MRI was technically inadequate in patients with atrial fibrillation and gave false positive findings of intravascular clot (one patient), and large atrial septal defect (two patients); TOE was good at showing the atrial situs and septum, the atrioventricular valves and coronary artery anatomy, but poor at showing the right ventricular outflow tract. Both TOE and MRI in combination were most valuable in patients with more complex anatomy, and least helpful in those with less complex anatomy (for example Fallot), when the main unanswered questions were the pulmonary artery pressure or the presence of coronary atherosclerosis.

In complex cases of congenital heart disease in adults, MRI and TOE combined are prerequisites for definitive anatomical and physiological diagnosis as they provide important and complementary information.

Permanent pacing in cardioinhibitory malignant vasovagal syndrome—the Westminster experience

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Thirty seven patients (mean age at implant 62·3 (SD 14·5); 21 men with cardioinhibitory malignant vasovagal syndrome have been managed with permanent pacemakers at the Westminster Hospital. They presented with syncope (mean (SD) 14·4 (29), frequency 3·4 (5·3)/year) and after conventional investigation they remained undiagnosed and without a generally accepted indication for pacemaker implantation. All developed vasovagal syncope with cardioinhibition (heart rate at syncope < 60 beats per min) during tilt testing performed according to the Westminster protocol (head up tilt at 60° on a footplate support for 45 minutes or until syncope intervenes). Dual chamber pacemakers were implanted in 37 (95%) and VVI pacemakers in the remaining two (5%). Follow up since implantation is complete for all patients (39 (19·9) months). Symptomatic improvement has been achieved in 84%, syncope abolished in 62%, and complete resolution of all symptoms is reported by 36%. The collective syncopal burden of these 37 patients has been reduced from 125·8 episodes each year to 12·6 episodes each year. One patient died from a myocardial infarction. The patients who have remained free of syncope since implant were younger (57·7 *v* 69·9 years, $p < 0{\cdot}02$) and had lower supine systolic blood pressure measurements at rest (135 *v* 162·7 mm Hg $p < 0{\cdot}001$) compared with those who have continued to experience syncope. Otherwise no demographic, clinical, investigative, or pacing variables suggested a more favourable outcome after pacing.

Our experience suggests that permanent pacing for cardioinhibitory vasovagal syncope is a reasonable therapeutic strategy. Over the mean follow up of 39 months, however, 38% of patients have experienced further syncope, and retrospective analysis failed to identify any preimplant variable which individually discriminates these patients from those who have remained free from syncope.

Sounds in the superior vena cava caused by presystolic flow reversal: a sign of right ventricular disease

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The classical S_4 is due to atrial flow into a diseased ventricle, but for some presystolic sounds, venous origin has been postulated. We therefore recorded phonocardiograms over the precordium, upper right sternal edge, and jugular veins with simultaneous electrocardiograms, Doppler flow in the superior vena cava, and atrioventricular valve flow in all patients referred for echocardiography over a nine month period. In 27 patients (10 with pulmonary hypertension, five dilated cardiomyopathy, three pericardial constriction, three cardiac amyloid, two hypertrophic cardiomyopathy, one aortic stenosis, one subaortic stenosis, one pericardial effusion with tamponade, and one after Mustard operation) presystolic sounds were recorded from a localised area (only over the superior vena cava or jugular veins). Each was associated with a rapid blood flow reversal in the superior vena cava, evident on Doppler. Presystolic sounds occurred at a point of change in acceleration (mean change = 17·1 (6·9) m/s^2 = 1·7 g). The onset of the sound coincided with peak retrograde velocity in 18 cases, peak forward velocity in six, and with the onset of retrograde flow in three. In 19 cases no atrial flow across either atrioventricular valve could be detected, excluding a classical S_4. In eight cases with atrial tricuspid flow, the sounds could only be recorded over the jugular veins.

Presystolic sounds may be recorded over the superior vena cava and jugular veins from patients with pulmonary hypertension and ventricular disease. They appear to originate from a rapid blood flow reversal in the superior vena cava rather than atrioventricular flow, and are thus quite different from the classical S_4.

Familial aggregation of idiopathic dilated cardiomyopathy: Variable clinical phenotypes and autosomal dominant pattern of inheritance in 14 families

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To establish a pattern of inheritance in familial dilated cardiomyopathy we assessed 117 apparently healthy relatives of 14 patients (probands) with dilated cardiomyopathy. Criteria for selection of pedigrees was based upon the presence of documented disease (World Health Organisation definition) in at least one other member of the proband's family. Twenty two family members were affected; 18 experienced disease related death (median age 47) with the clinical diagnosis confirmed at necropsy in 13. All 117 apparently healthy relatives were screened with a standard 12 lead electrocardiogram and cross sectional echocardiogram and were classified either as unequivocally normal or as carriers. The latter had either an abnormal electrocardiogram or at least one echocardiographic measurement of left ventricular cavity dimension, or % fractional shortening outside 2 SD of normal (measurements corrected for body surface area). Fourteen of the 117 relatives (12%) had systemic hypertension and were excluded from the study. Thirty two of the remaining 103 relatives (31%) were classified as carriers and underwent 24 hour Holter monitoring and maximal treadmill exercise (Naughton protocol). Of these 32 relatives, four (aged 45 (21) had only abnormal electrocardiograms; 18 (aged 24 (13) had normal electrocardiogram and abnormal cross sectional echocardiogram with 10 (5)% left ventricular enlargement, but % fractional shortening within the normal range; 10 (aged 41 (13)) had abnormal electrocardiogram and cross sectional echocardiogram with 16 (21)% left ventricular enlargement from normal and 26 (9)% fractional shortening. Three of these 10 relatives also had ventricular arrhythmia (Lown class III or IV).

Thus non-invasive techniques identified asymptomatic cases of familial dilated cardiomyopathy among apparently healthy relatives of patients with the disease. Pedigree analysis was most consistent with an autosomal dominant pattern of inheritance with a high degree of penetrance.

Value of time and frequency domain and spectral temporal mapping analysis of the signal-averaged electrocardiogram in identification of patients with hypertrophic cardiomyopathy at increased risk of sudden death

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Late potentials detected by the signal-averaged electrocardiogram (SAECG) identify postinfarction patients at risk from sustained ventricular tachycardia and sudden death. Hypertrophic cardiomyopathy is also associated with increased risk of sudden death. In adults, episodes of non-sustained ventricular tachycardia on ambulatory electrocardiographic monitoring are a marker of high risk patients. In children and adolescents, however, no reliable electrocardiographic marker exists and clinical features have low predictive accuracy. The prognostic value of the SAECG in hypertrophic cardiomyopathy has not been systematically evaluated. In this study, we examined the relation of detailed time domain, frequency domain, and spectral temporal mapping analysis of the SAECG and clinical and echocardiographic features, and the results of 48 hour ambulatory electrocardiographic monitoring in 121 consecutive patients with hypertrophic cardiomyopathy but no cardioactive medication. Non-sustained ventricular tachycardia on Holter monitoring was recorded in 27 (23%) patients. Late potentials were detected on the time domain SAECG in three (11%) patients with ventricular tachycardia *v* three (3%) without (NS). Of the SAECG variables, reduced (< 150 μV) voltage of the initial 40 ms of the signal averaged QRS complex was the best predictor for non-sustained ventricular tachycardia (sensitivity, 95%; specificity, 74%; positive predictive value, 64%; negative predictive value, 97%). The frequency domain analysis and spectral temporal mapping of the SAECG did not improve the identification of patients with ventricular tachycardia. Eight patients (of whom seven were ≤30 years of age) experienced catastrophic events: three died suddenly and five were resuscitated from out of hospital ventricular fibrillation. None of them had an abnormal SAECG.

Alterations of the initial portion of the signal-averaged QRS complex identified adults with hypertrophic cardiomyopathy and non-sustained ventricular tachycardia on ambulatory monitoring, but the SAECG was not useful in identifying those young patients who suffered cardiac arrest.

Enteroviral serology in idiopathic dilated cardiomyopthy

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Serological studies provide the principal supporting evidence for a pathogenic role of enteroviral infection in human idiopathic dilated cardiomyopathy (DCM). These studies, however, have failed to study matched controls taken at the same time and from the patients' environment and to distinguish between active and previous viral infection. In this study we applied a reverse radioimmunoassay technique for the detection of coxsackie B virus specific-immunoglobulin M (CBV IgM) (B1–5) to sera taken from patients with DCM at the time of diagnosis (n = 83), matched controls (n = 17), and unmatched family members (n = 94). Sera from 32 patients with DCM and 11 matched controls was also assessed for the presence of a common enteroviral antigen (VP1) believed only to be present during persistent active viral infection. Patients with DCM (mean age 44·2, range 17 to 74) had been symptomatic for 38·6 (49) months, 18 (22%) gave a history of a preceding acute viral illness and three had features of myocarditis on endomyocardial histology. Positive CBV IgM serology was seen in 24 (29%) patients with DCM, three (18%) matched controls ($p = 0{\cdot}17$), and 16 (17%) unmatched controls ($p = 0{\cdot}03$). No association was found in patients with DCM between the presence of positive CBV IgM serology and clinical or histological features. Serological responses were most commonly against serotypes B2 and B5; however multitypic responses to a number of different viral serotypes were common (14/48, 29%). These responses were similar in patients with DCM and control groups. High concentrations of VP1 were detected in 7/32 (22%) patients with DCM compared with 0/11 matched controls ($p = 0·1$). There was no association between the presence of high concentrations of VP1, clinical and histological features, or positive CBV IgM ($R = 0·1$, $p = 0·8$).

This study shows that (*a*) CBV IgM is common within the general population, (*b*) a higher prevalence of CBV IgM in patients with DCM compared with unmatched controls, (*c*) a non-significant trend towards a higher prevalence of CBV IgM and VP1 in patients with DCM compared with matched controls, and (*d*) no association in DCM between positive enteroviral serology and clinical or histological features.

Mechanisms of intracellular pH recovery in perfused heart

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The sodium-hydrogen (Na^+-H^+) antiport has been suggested as the predominant, or only mechanism facilitating recovery from an intracellular acidosis in cardiac muscle. In other mammalian cells external bicarbonate (HCO_3^-) dependent acid equivalent extrusion and proton (H^+) coupled lactate efflux can also participate. We have examined the contributions of these three mechanisms to the recovery of pH_i and contraction after an acid load induced at normal extracellular pH with either an ammonium chloride (NH_4Cl) prepulse or 1-lactate, in the Langendorff-perfused ferret heart. Hearts were perfused with either HCO_3^- or nominally HCO_3^- free (HEPES) buffer. The Na^+-H^+ antiport was blocked by the specific inhibitor ethylisopropylamiloride. pH_i was estimated using ^{31}P nuclear magnetic resonance spectroscopy with isovolumic left ventricular developed pressure being recorded throughout. Hearts were exposed to either NH_4Cl (10 mM) or 1-lactate (10 mM) for 10 min and rates of recovery of pH_i from 6·90 after withdrawal of NH_4Cl or 1-lactate calculated. Results are expressed as mean (SE). After an intracellular acidosis induced by an NH_4Cl prepulse the initial rate of recovery of pH_i in Hepes solution was slower (0·013 (0·005); $n = 14$) than in HCO_3^- solution (0·024 (0·006); $n = 13$). Na^+-H^+ antiport inhibition delayed pH_i recovery in HCO_3^- solution (0·012 (0·003); $n = 9$) and blocked pH_i recovery in Hepes solution ($< 0·001$; $n = 10$). Recovery of left ventricular developed pressure was similar to that of pH_i with Na^+-H^+ antiport inhibition causing slowing of recovery in HCO_3^- solution and blocking recovery in Hepes solution. After 1-lactate withdrawal pH_i recovered more rapidly (0·047 (0·005); 13) as did left ventricular developed pressure than after an NH_4Cl prepulse and both recovered fully in the absence of external HCO_3^- during Na^+-H^+ antiport inhibition. H^+-coupled lactate efflux can account for the differences in recovery after 1-lactate when compared with recovery after NH_4Cl prepulse.

The Na^+-H^+ antiport and an external HCO_3^- dependent mechanism are therefore both important in the recovery from intracellular acidosis in the intact perfused ferret heart. When intracellular lactate is high, for example, after ischaemia, H^+-coupled lactate efflux could also contribute to this recovery.

Characterisation of the angiotensin receptor expressed by cells transfected with a plasmid containing the AT_1 cDNA

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Angiotensin II (AII) is an important peptide in cardiovascular disease, yet little is known about regulation of its receptor at the molecular level. Two AII receptor subtypes, AT_1 and AT_2, have been identified using non-peptide antagonists and the complementary DNA (cDNA) encoding the AT_1 receptor has been isolated. We have examined the pharmacological profile and signal transduction pathways of this cloned receptor transiently expressed in COS-M6 cells. Transfected COS-M6 cells expressed high specific (^3H)-AII binding (K_d of 7·1 (0·5) nM and B_{max} of 1·9 (0·5) pmol/mg protein, $n = 5$). Competition binding assays showed that the receptor displayed high affinity for AII, AIII, and the AT_1 selective antagonist DuP753 (K_i values of 2·4, 13·6, 12·1 nM, respectively), but low affinity for the AT_2 selective drugs CGP42112A and PD123177 (K_i values > 1000 and $> 10\,000$ nM respectively). The AT_1 receptor has been reported to couple to two signal transduction pathways, the mobilisation of intracellular calcium ($Ca^{2+}{}_i$) and inhibition of adenylate cyclase. Addition of AII (0·1 μM) to transfected cells resulted in a transient increase in $(Ca^{2+})_i$ (from 57 (8) to 303 (26) nM, $n = 20$). By contrast, AII (0·1 μM) failed to attenuate forskolin (1 μM) induced increases in intracellular cyclic AMP, suggesting that the cDNA encodes at AT_1 receptor coupled to the mobilisation of $(Ca^{2+})_i$, but not coupled to inhibition of adenylate cyclase. Cells not transfected did not express AII receptors, nor a calcium response to AII.

We have transiently expressed the angiotensin AT_1 receptor and defined its pharmacology and coupling to mobilisation of $(Ca^{2+})_i$, and can now therefore study its structure and regulation using site directed mutagenesis.

Programmed cell death is a mechanism of senescence of human endothelial cells in culture

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Programmed cell death (apoptosis) has been shown to be an important mechanism of physiological senescence in a number of cell types including neutrophils, lymphocytes and most epithelial cell types. The exact cellular mechanisms of apoptosis remain unclear, but a final common event is activation of an endogenous endonuclease, causing highly organised digestion of double stranded DNA at internucleosomal sites, which produces a characteristic "ladder pattern" on DNA electrophoresis. This pattern is thought to be specific to cells dying by apoptosis rather than by necrosis. Endothelium grown from a number of sources appears to have a finite life, limited to a specific number of population doublings in culture. It was investigated whether apoptosis is the mechanism of death in human umbilical vein endothelial cells (HUVEC) grown to end of life in culture; HUVEC were grown in culture with medium 199 supplemented with heparin and endothelial cell growth supplement. Growth appeared to cease after the third passage of the cells in culture. The cells were rounding up and some had floated off into the supernatant medium. Cells were harvested both from the medium and separately from the floor of the culture flasks; DNA was extracted using a phenol/chloroform technique with proteinase K digestion; and RNA was removed using an RNase A digestion. One per cent agarose gel electrophoresis showed no evidence of DNA cleavage in the cells that remained adherent but a characteristic DNA ladder was seen from the cells in the supernatant. A spontaneously immortalised HUVEC line (ECV 304) was also studied. These cells, which retain phenotypic characteristics of endothelium, have been grown in culture for over a hundred passages. Exposure to tumour necrosis factor (200 ng/ml) was without morphological effect and no DNA fragmentation could be found. Calcium ionophore (A23187) (10 μM) as well as the protein kinase C antagonist H-7 (50–200 μM) caused rounding up of these cells and detachment from the culture plate but no DNA fragmentation.

These results suggest that apoptosis may be an important mechanism limiting the absolute life span of endothelial cells.

Flow cytometry of whole blood: a method for analysing platelet activation in cardiovascular disease

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Platelets are important in the pathogenesis of cardiovascular disease. Activation of platelets results in thrombus formation and the release of platelet derived growth factors, vasoactive and pro-coagulant molecules. Assessment of platelet activation by aggregometry is insensitive, whereas detection of released β thromboglobulin or platelet factor 4 is subject to technical error and only measures platelet degranulation. Platelets are activated by a number of physiological agonists. Weak agonists such as adrenaline or ADP cause a conformational change in the glycoprotein (GP) IIb–IIIa complex, exposing a binding site for fibrinogen. Strong agonists such as thrombin or vessel wall collagen cause degranulation that results in the translocation of granule membrane to the platelet surface, bringing with them specific membrane proteins which appear as neo-antigens, and can be detected with monoclonal antibodies (MAbs). Two such MAbs are described, RFAC4 recognises the GP53 antigen on lysosomal membranes and RFAC2 recognises the GMP140 antigen of the α granule. These MAbs were labelled with fluorochrome and used in a whole blood flow cytometric assay to detect activated platelets minimising the artefactual activation in vitro. Fibrinogen bound to activated GPIIb—IIIa was detected using an anti-fibrinogen antibody. None of the activation markers was expressed on resting platelets from normal subjects (n = 15). After stimulation with ADP >80% of normal platelets bound fibrinogen, 10% bound RFAC4, and <2% bound RFAC2. When stimulated with thrombin >90% of normal platelets expressed all three markers. Platelets from patients with different thrombotic disease states showed different patterns of expression of the three activation markers. Blood from patients with peripheral vascular disease (n = 13) contained platelets with raised GP53 expression. This increased expression was enhanced when ADP was added to the blood ex vivo. By contrast, patients with unstable angina (n = 6) showed more activation, with raised expression of all three markers.

The differential expression of the various activation markers can be used to assess the extent of platelet involvement in various thrombotic states and to gain information as to the likely cause of activation in vivo. This information will lead to a more rational approach to antiplatelet therapy.

Electrocardiographic waves following the T wave in patients with idiopathic ventricular tachycardia: a surface manifestation of afterdepolarisations?

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The mechanisms of arrhythmia in patients with idiopathic ventricular tachycardia remain unclear, though there are suggestions that the mechanism may be triggered by activity in patients with exercise induced ventricular tachycardia. We have examined the electrocardiogram during exercise tests in 20 patients with idiopathic ventricular tachycardia for evidence of a triggered activity mechanism. Eight patients (six with exercise induced ventricular tachycardia) showed prominent deflections either in the tail portion of the T wave, or after the T wave in the position of the classical U wave. Visualisation of these deflections was easier using high gain (20 mm/mV) and the filtered average complex, available on the Marquette treadmill exercise test machine. These deflections were most clearly seen in chest leads V2 to V4 in all patients and although clearly visible at rest, became larger in the recovery period after exercise. During the exercise test, the deflections became difficult to identify because of the presence of the next P wave in the tail of the T wave. The mean amplitude of the deflections was 2·4 (0·8) (SD) mV, and the amplitude of the associated T wave was 3·9 (2·5) mV. The time from the Q wave to the peak to the T wave was 287·5 (68·4) ms and from the Q to the peak of these deflections was 447·5 (72·7) ms. The time from the Q to the next P wave was greater than 600 ms in all cases where the measurements were performed. In six patients, ventricular extrasystoles were identified in association with the deflections; the Q to extrasystole coupling interval was never more than 40 ms different from that of the Q to peak of the deflection. The deflections were not completely abolished by calcium antagonists or β blockers. We propose that these deflections may represent a surface manifestation of membrane potential oscillations after the action potential, i.e. afterdepolarisations, which are identifiable by use of the averaged, filtered, high gain electrocardiogram.

The close relation in timing to ventricular extrasystoles suggests that these may play a part in triggered ventricular extrasystole activity.

Relation of ventricular ectopic activity to spectral measures of heart rate variability in patients with idiopathic ventricular tachycardia

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The autonomic nervous system appears to have an important role in the genesis of ventricular arrhythmias in patients after myocardial infarction and in idiopathic ventricular tachycardia. Roughly 40% of patients with idiopathic ventricular tachycardia have the arrhythmia induced at exercise. Spectral measures of heart period variability allow a non-invasive estimate of the activity of sympathetic and parasympathetic efferents to the heart. We have studied the relation of hourly spectral measures of heart period variability to the occurrence of ventricular extrasystole in 20 patients with idiopathic ventricular tachycardia (age range 17 to 60). Twenty four hour Holter tapes were obtained from patients in a drug free state and analysed on the Marquette 8500 laser Holter system. Spectral measures obtained from the heart period variability program were the low frequency components (L) (0·04–0·15 Hz) representing predominantly sympathetic tone (S) with some contribution from the parasympathetic and high frequency components (H) (0·15–0·4 Hz) representing mainly parasympathetic tone (P). High sympathetic tone was defined as $H > 12$ and high parasympathetic tone as $L > 30$. The occurrence of single ventricular extrasystoles was ignored by the program with interpolation of the RR intervals, whereas longer episodes of extrasystole are excluded. On an hourly analysis of spectral components in relation to ventricular extrasystole, extrasystoles occurred significantly more often during periods of low S and low P tone ($F = 20{\cdot}5$, $p < 0{\cdot}0001$). The number of extrasystoles did not differ statistically in the other combinations of S and P tone (Mean extrasystole/hour (SEM) high S and high P, 204·9 (17·7); low S and high P, 338·4 (58·9), high S and low P, 180·1 (36·8); low S and low P 612·8 (50·1). The ventricular extrasystoles were not escape beats as the coupling interval of the extrasystole to the previous normal beat was less than the previous normal to normal interval.

Ventricular extrasystoles are more frequent during periods of low sympathetic and low parasympathetic tone and are decreased in number when either sympathetic or parasympathetic activity is increased in patients with idiopathic ventricular tachycardia.

Development of late potentials after myocardial infarction is related to infarct size

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Recent studies have shown a reduction in the incidence of late potentials after thrombolysis, but the mechanism for this remains unclear. One possible explanation is that late potential development is related to infarct size, but previous studies attempting to relate late potentials to infarct size using peak creatinine kinase or its MB isoenzyme have produced conflicting evidence. A prospective study was therefore undertaken to relate late potentials measured from the signal-averaged electrocardiogram to infarct size measured by the cumulative release of α-hydroxybutyrate dehydrogenase (α-HBDH). Sixty six patients admitted with a first myocardial infarction were studied. Blood samples were taken on admission, every 12 hours for the first two days and daily for the next three days. The samples were analysed for α-HBDH activity and the area under the time activity curve up to 72 hours was calculated as an index of infarct size. Signal averaged electrocardiograms were performed on day 1, day 3, day 7, and at six weeks after admission. The presence of late potentials was assessed according to conventional time domain analysis criteria. The incidence of late potentials overall was 18·6% on day 1, 22·7% on day 3, 36·5% on day 7, and 21·7% on day 42. The mean area under the curve of the patients' late potential positive and late potential negative on each of these days was 30 443 *v* 18 254 on day 1 ($p < 0{\cdot}05$ by *t* test), 31 689 *v* 17 077 on day 3 ($p < 0{\cdot}05$), 27 148 *v* 18 970 on day 7 (non-significant), and 36 680 *v* 17 613 on day 42 ($p < 0{\cdot}01$).

Late potentials are related to infarct size. By inference reduction of infarct size by reperfusion may be the mechanism by which thrombolysis reduces the incidence of late potentials.

Magnesium prolongs ventricular action potential duration in the denervated heart

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The empirical use of magnesium (Mg) as an antiarrhythmic agent has been reported for over 50 years, but the mechanism of such beneficial effect remains obscure. We postulated that subtle changes in ventricular electrophysiology would be more apparent in the denervated heart, known to be supersensitive to catecholamines and adenosine. Ventricular monophasic action potentials were recorded from the right ventricular pacing in 10 of 12 unselected cardiac transplant recipients (age 37 to 61 y). Median time from transplantation was 15 weeks (range 1 to 35). All patients were receiving standard immunosuppressive treatment and none was treated with antiarrhythmic drugs. Serum potassium and calcium concentrations were within normal limits. Ventricular action potential duration was recorded and the ventricular effective refractory period established at two paced rates, before and after intravenous administration of 8 mmol magnesium sulphate. A 12 lead electrocardiogram was recorded before and after each procedure. Mean (SD) serum magnesium concentration rose twofold; 0·69 (0·08) *v* 1·31 (0·23) mmol/l ($p < 0{\cdot}001$). There was a strong trend towards prolongation of the ventricular action potential duration in response to Mg (95% CI, 1·3 to 12·0 ms; $p = 0{\cdot}11$). No consistent effect on ventricular effective refractory period was noted. Duration of QRS interval was prolonged in eight out of 11 patients ($p < 0{\cdot}07$; paired *t* test; 90% CI, 0·8 to 13·6 ms), showing, or exacerbating a right bundle branch block pattern. There was no significant difference in the QTc interval. Baseline hypomagnesaemia (serum $Mg < 0{\cdot}70$ m mol/l) was concurrent in five subjects; there was no difference in ventricular action potential at baseline pacing between hypo- and normo-magnesaemic recipients. Mean ventricular effective refractory period, however, during both pacing protocols was significantly shorter both before and after Mg in the hypomagnesaemic group ($p < 0{\cdot}05$; ANOVA).

Intravenous magnesium measurably prolongs ventricular action potential in the denervated human heart and this effect is independent of baseline magnesium. Such effects are predicted from single cell studies, but have not been previously shown in man.

A 10 year review of the management of false aneurysms after transfemoral arterial catheterisation

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False aneurysms of the femoral artery are an infrequent complication of transfemoral arterial catheterisation. They may be the cause of significant morbidity but little is documented about their clinical course and the results of surgical repair. The management by one vascular surgery unit of these false aneurysms over the decade commencing 1 January 1980 was reviewed. Fifty five false aneurysms were identified; three after 3396 radiological procedures (0·09%) and 52 after 11 255 cardiac procedures (0·46%). Three false aneurysms did not require surgical repair and one patient died before treatment. Twenty false aneurysms remained stable, 18 continued enlarging, and 13 had ruptured at the time of operation. Aetiological factors and postoperative complications of the different groups were analysed using the χ^2 test. The mean time to presentation for stable false aneurysms was 4·05 days (SD 5·46), for enlarging false aneurysms 27 days (66), and for ruptured false aneurysms 2·75 days (1·65). Postoperative complications developed in four (20%) stable, four (22%) enlarging and seven (58%) ruptured ($p < 0{\cdot}05$). There was one postoperative mortality but this resulted from the complications of subsequent cardiac surgery. Rupture of false aneurysms was associated with raised liver function tests (LFTs) on admission ($p < 0{\cdot}01$), pre-catheterisation warfarin therapy ($p < 0{\cdot}05$) and peripheral vascular disease ($p < 0{\cdot}05$).

False aneurysms often present late after transfemoral arterial catheterisation. Ruptured false aneurysms are seen earlier than non-ruptured false aneurysms and are associated with significantly greater morbidity. Patients with false aneurysms who have elevated LFTs, peripheral vascular disease, or were taking warfarin are at an increased risk and merit closer observation and perhaps earlier intervention.

Clinical features and treatment of patients with paroxysmal atrial fibrillation: the CRAFT multicentre registry

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Epidemiologic data of clinical features, and survey of the use of antiarrhythmic drug therapy in patients with symptomatic paroxysmal atrial fibrillation were obtained. Clinical and echocardiographic data on all eligible outpatients seen by cardiologists at the 10 centres participating in the CRAFT (Controlled Randomised Atrial Fibrillation Trials) studies were registered. All 113 patients had had at least one episode of atrial fibrillation in the previous six months. Sixty two (55%) were men, mean age 56·0 (SD 13·9) and 51 were women, mean age 63·8 (SD 11·9). Symptom frequency with no antiarrhythmic treatment was similar between the sexes: 15 (13%) had no episodes, 36 (32%) had 1 to 2 episodes, and 61 (54%) had more than two episodes in two months. Clinical findings (cardiovascular history, physical examination) were normal in more men than women: 37 (60%) *v* 20 (39%) had no abnormality ($p < 0{\cdot}05$), 13 (21%) *v* 16 (31%) had minor abnormalities such as untreated hypertension or "benign" murmurs, and 12 (19%) *v* 15 (29%) had significant abnormalities. Detailed echocardiographic findings were available for 45 men and 32 women: again, these were entirely normal in a greater proportion of men than women (26 (59%) *v* 13 (40%), $p < 0{\cdot}05$). The difference was entirely accounted for by a greater incidence of mitral valve prolapse among the women (six (19%), *v* one (2%)): the incidence of other minor valve abnormalities (16%), significant valvular disease (16%), and myocardial disease (9%) was identical between the sexes. Left atrial diameter was increased (4·0 cm or greater) in eight women (25%) and three men (7%). Sixty seven patients (59%) were taking prophylactic antiarrhythmic drugs. Of these, 30% were taking digoxin, 7% class 1a drugs, 12% class 1c drugs, 15% β blockers, 12% sotalol, 7% aminodarone and 9% combinations. The class of symptom frequency was improved by treatment in 25 (37%), unchanged in 35 (52%), and worsened in 7 (10%).

Paroxysmal atrial fibrillation occurs at a lower age and more often as an isolated finding in men compared with women. Most treatment is with drugs that have not been formally evaluated for this condition, and controlled trials of these agents are needed.

Coronary artery bypass grafting; identification of "fast track" patients

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Availability of intensive therapy beds often determines the throughput of cardiac surgery. The prospective identification of patients who spend less than 24 hours in intensive therapy, "fast track" patients, would allow optimal bed usage and efficient planning of operating lists. Potential fast track patients were identified from 421 patients (16% women, mean age 57 (8) years), admitted to intensive therapy after coronary surgery over a nine month period, according to prospectively defined criteria: good left ventricular function (ejection fraction >50%), stable angina, age <60, and absence of obesity (body mass index <30), diabetes, or other serious pathology. Eighty seven (21%) patients were predicted as fast track; 79 (91%) spent less than 24 hours in intensive therapy, but four spent >72 hours in intensive therapy. The positive predictive accuracy of these criteria for the identification of fast track patients was 91% but the sensitivity was low at 23%. Of the remaining 334 patients, 261 (78%) spent less than 24 hours in intensive therapy, 121 (36%) had unstable angina, and 87 (26%) had left main stem stenosis. The positive predictive accuracy of good ventricular function alone was 85% (75% sensitivity), one or two vessel disease was 91% (35% sensitivity), and left ventricular end diastolic pressure <13 mm Hg was 91% (59% sensitivity). These associations were all significant ($p < 0{\cdot}05$). Age, sex, left main stem stenosis, unstable angina, body mass index, diabetes, and treadmill exercise tolerance were not significantly associated with time spent in intensive therapy.

Fast track patients can be identified prospectively with high predictive accuracy from clinical criteria. The relative insensitivity of these criteria is unimportant when planning operating lists because only a subset of intensive therapy beds need to be designated as fast track. Left ventricular function, especially as measured by left ventricular end diastolic pressure, and number of coronaries diseased were the best individual predictors of fast track patients.

Angiographic and pathological features of coronary occlusive disease in cardiac transplant patients

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Coronary occlusive disease is the commonest late complication after cardiac transplantation. It has both similarities and differences compared with conventional atherosclerotic coronary disease. The pathophysiology and risk factors associated with disease development are not completely clear at present. Angiographic and pathological data for coronary occlusive disease in our cardiac transplant programme were reviewed. Of a population of 383 patients whose transplant was performed between January 1979 and June 1990, 447 coronary angiograms were available for review in 193 cardiac transplant patients. Coronary occlusive disease was defined as any evidence of disease in a primary or secondary coronary artery. The angiographic prevalence of coronary occlusive disease was 3% and 40% at one and five years respectively. Twenty six grafts failed due to coronary occlusive disease compared with 132 graft failures from all causes during this period. Thirteen of a possible 18 post mortems from patients dying from coronary occlusive disease were available. The remaining seven patients underwent cardiac retransplantation with one patient undergoing a further cardiac retransplant. Acute thrombosis was present in a large vessel in seven of 13 fatal cases undergoing necropsy (54%). Significant large vessel involvement with disease in smaller distal vessels on histological exmination was present in four patients (31%). The remaining two patients (15%) had small vessel disease alone. Twelve of the 13 patients had significant cardiomegaly (cardiac weight ≥400 g) with a mean weight of 510 g (range 370–740 g). Risk factors associated with disease development in multivariate analysis included donor age >40 (RR 3·22, CI 0·94–10·98, p < 0·1), recipient age >50 (RR 1·74, CI 0·77–3·91, p < 0·1), and a previous history of ischaemic heart disease (RR 2·71, CI 1·4–5·22, p < 0·05).

Coronary occlusive disease is the main late complication after cardiac transplantation. Coronary thrombosis, ischaemia from large and small vessel coronary stenoses plus cardiomegaly cause graft failure in these patients.

High levels of antistreptokinase antibody and neutralisation titres from three days to three years after a previous dose of streptokinase

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Streptokinase (SK) reduces mortality in acute myocardial infarction. Its antigenicity can cause allergic reactions, or SK neutralisation, or both resulting in suboptimal or ineffective treatment. Currently, readministration of SK is not advised from five days to one year after a previous dose. We have conducted a study to determine when SK can be readministered for reinfarction by measuring both antistreptokinase antibody (AB) and neutralisation titres (NT) in two groups of patients: (*a*) early—36 patients (18 received hydrocortisone, HCO group, before thrombolysis and 18 did not, non-HCO group) whose titres were measured before and daily for at least five days after thrombolysis. (*b*) late—32 patients who received thrombolysis 12 to 38 months previously. Results are mean (SEM): (*a*) early—in 33% of non-HCO and 5·6% of HCO patients, the AB, or NT, or both were raised by day 4. One patient could neutralise 1·97 MU of SK at day 4 and 15·75 MU by day 5. Non-HCO group: day 4, AB 57 (19), NT 0·24 (0·10) MU; day 5, AB 226 (76), NT 1·33 (0·85) MU; HCO group: day 4, AB 21 (8), NT 0·13 (0·01) MU; day 5, AB 47·8 (17), NT 0·16 (0·03) MU. (*b*) late—16 patients (50%) had either AB ≥ 160, or NT > 1·5 MU, or both; 12 to 17 months: AB 230 (51), NT 0·84 (0·25) MU; 18 to 29 months: AB 193 (55), NT 0·50 (0·16) MU; 30 to 38 months: AB 56 (26), NT 0·16 (0·03). Anti-SK AB and NT were correlated (n = 255, r = 0·91, p < 0·001).

It would be prudent to avoid the readministration of streptokinase or anistreplase between three days and at least three years two months after a previous dose.

Heart rate recovery after exercise: a new index of autonomic balance in post-infarction patients?

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Depressed baroreceptor sensitivity (BRS) is associated with an increased risk of spontaneous and inducible life threatening arrhythmias after myocardial infarction. Its assessment, however, is time consuming. As the rate of decline in heart rate after exercise is influenced by parasympathetic function, we examined whether baroreceptor sensitivity in post-infarction patients could be estimated from a record of the heart rate during the recovery period after predischarge treadmill exercise tests. In a prospective study, 56 patients aged between 30 and 70 underwent baroreceptor sensitivity testing immediately before a maximal treadmill exercise test. Investigations were conducted between six and 11 days after infarction. Resting systolic blood pressure, peak systolic blood pressure, resting heart rate, peak heart rate, and exercise duration were recorded. A continuous plot of instantaneous heart rate against time was made throughout exercise. The rate of decline in heart rate was defined as the slope of the rapid, linear, early recovery phase and expressed in beats/min/s. Duration of exercise ranged from 90 to 623 s; depressed baroreceptor sensitivity from 1·4 to 35 ms/mm Hg (mean 9), peak heart rate from 81 to 172 beats/min, and rate of decline of heart rate from 0·05 to 1·1 beats/min/s. Depressed baroreceptor sensitivity correlated with rate of decline of heart rate (r = 0·45, p < 0·01), and with resting heart rate (r = 0·37 p < 0·01), and this regression equation was found: depressed baroceptor sensitivity = ((10·8 × rate of decline of heart rate) − (0·2 × resting heart rate) + 20). Depressed baroreceptor sensitivity did not correlate with diastolic blood pressure, peak heart rate, or resting systolic blood pressure.

The rate of decline in heart rate after exercise may be used to assess vagal reserve. Its value in predicting sudden death needs further study.

Evidence for free radical generation (oxidative stress) in unstable angina

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The pathophysiology of unstable angina seems to involve the formation of, and then spontaneous lysis of, coronary artery thrombosis. Consequently, recurrent myocardial ischaemia reperfusion cycles may occur with the potential for free radical generation. We have, therefore, sought evidence of oxidative damage to proteins by measuring plasma reduced thiol, and lipids by measuring plasma thiobarbituric acid reactive substances, in patients with unstable angina. Unstable angina was defined as crescendo or rest ischaemic cardiac pain associated with electrocardiographic change but no rise in cardiac enzymes. Patients with chronic stable angina admittted for elective cardiac catheterisation were used as controls (for medication, smoking history, etc); a normal population was also studied. Forearm venous blood was collected at 0830 hours after an overnight fast. In unstable angina (n = 25; age 57 (2); nine women) mean plasma reduced thiol concentration was reduced to 419 (9) (SEM) compared with 485 (4·9) μmol/l in patients with stable angina (n = 24; age 58 (2); three women) (p < 0·01)). Plasma reduced thiol concentration in normal people was 564 (8) μmol/l (p < 0·01 *v* both angina groups). Thiobarbituric acid reactive substances were similar in each angina group (unstable angina 10·00 (0·37) *v* stable angina 9·6 (0·21) nmol/l (NS)). The mean concentration of thiobarbituric acid reactive substances in normal people was 8·1 (0·21) nmol/l (p < 0·01 *v* both angina groups). The extent of coronary artery disease was not different in the two patient groups.

These data show that unstable angina is associated with oxidative damage to plasma proteins, possibly due to free radical production. Free radical activity could have detrimental effects in unstable angina by damaging endothelium and promoting thrombosis.

Significance of reciprocal ST depression on the resting and exercise electrocardiogram in patients with acute infarction treated by thrombolysis

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Reciprocal ST segment depression is commonly found in acute myocardial infarction but its significance remains controversial and it does not usually influence management strategies. When reciprocal ST depression occurs during predischarge exercise testing, however, it may lead to referral for further investigation, though whether it represents remote ischaemia has not been established. We have prospectively studied 153 patients with acute myocardial infarction treated by thrombolysis within 12 hours of the onset of chest pain. All underwent early exercise testing and 98 also had coronary arteriography. Reciprocal ST depression on the presenting electrocardiogram was found in 67% of patients and was strongly associated with the time from onset of chest pain, those with reciprocal change presenting significantly earlier than those without (3·4 (0·2) *v* 5·3 (0·4) hours, p < 0·001). Importantly there was no relation between reciprocal change and multivessel disease or patterns of regional wall motion abnormality. During predischarge exercise testing, reciprocal ST depression occurred in 15% of patients, and isolated ST elevation and depression occurred in 12% and 30%, respectively. Patients with reciprocal ST depression all had Q wave infarcts, and were more likely to have persistent occlusion of the infarct related artery (48% *v* 27%, p < 0·05), and either akinetic or dyskinetic regional left ventricular wall motion (71% *v* 42%, p < 0·01). Importantly, there was no association between reciprocal ST change on the exercise electrocardiogram and multivessel disease.

Reciprocal ST depression in acute myocardial infarction is a passive electrical phenomenon and not a sign of multivessel disease. When it occurs on the presenting electrocardiogram it usually reflects very recent coronary occlusion, being uncommon in patients who present late. Reciprocal change on the predischarge exercise electrocardiogram reflects extensive Q wave infarction and is not an indication for tertiary referral.

Neurohumoral activation after acute myocardial infarction: differences between the systems and with different drug treatment

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Acute myocardial infarction has been shown to be associated with activation of several neurohumoral systems. The integrated response of these systems at rest and during exercise is less well documented. In this study we have compared plasma noradrenaline, atrial natriuretic peptide, and plasma renin activity in a group of patients who had recently suffered a myocardial infarction with a group of normal control subjects.

Forty eight patients (five women), mean (SEM) age 57·5 (1·3), were studied 18 (0·8) days from a Q wave myocardial infarction, together with nine normal subjects aged 54·2 (2·8). Noradrenaline, atrial natriuretic peptide and plasma renin activity were measured at rest, at submaximal, and symptom limited treadmill exercise. Atrial natriuretic peptide was significantly higher at rest (p < 0·005) and during exercise (p < 0·02) in the patients compared with the normal people. In the patients (n = 21) taking prophylactic β blockers, values were the same as in the other patients at rest, but were higher (368·7 (64·2) *v* 158·2 (23·8) pg/ml p < 0·005) than at symptom limited exercise. Plasma renin activity was no different between the patients and controls at rest or during exercise. Not surprisingly those patients taking diuretics (n = 10) had higher values at rest (2·85 (0·6) *v* 0·98 (0·18) ng/ml/h p < 0·001) and during exercise (4·36 (0·89) *v* 1·68 (0·32) ng/ml/h p < 0·001) compared with the remaining patients. Noradrenaline concentration was no different between the patients and the controls either at rest or during exercise. The patients taking diuretics did, however, have higher concentrations than the controls at submaximal exercise (1285 (247) *v* 632 (72) pg/ml at stage 1 and 1044 (105) *v* 693 (95) pg/ml at stage 3 of the exercise protocol (both p < 0·05). Patients on diuretics had higher resting concentrations than the remaining patients at rest (933 (114) *v* 650 (42) pg/ml, p < 0·01) but not during exercise.

The neurohumoral response to acute myocardial infarction was largely resolved, both at rest and during exercise, 18 days after acute myocardial infarction, β blockers caused an unexpected increase in atrial natriuretic peptide during exercise without affecting the other hormones. Those patients taking diuretics had, not surprisingly, increased concentrations of plasma renin activity and noradrenaline.

Contrasting effects of isoprenaline and calcitonin gene related peptide on intracellular free calcium concentrations in isolated depolarised cardiac myocytes

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Initial events in ischaemic injury to the myocardium include cellular depolarisation causing intracellular sodium and calcium overload. Calcium overloaded cells exhibit after-depolarisations and after-contractions, which enhance the conditions for abnormal ventricular rhythms. Ultimately cellular calcium overload results in irreversible changes in cellular metabolism and cell death. A study of the regulation of intracellular calcium is therefore important for the prevention of ischaemic cellular injury and arrhythmias. We have examined the effect of isoprenaline and calcitonin gene related peptide (CGRP) upon intracellular free calcium concentrations ($[Ca^{2+}]_i$) in partially depolarised calcium overloaded single cardiac myocytes. Isolated myocytes were prepared by enzymatic digestion and studied in an external solution of composition (mM) NaCl 112, $NaHCO_3$ 24, NaH_2PO_4 1, KCl 5·4 $MgCl_2$ 1, HEPES 5, glucose 10; pH 7·4 with NaOH. Cells were loaded with the esterified form of the calcium sensitive fluorescent dye fura 2/AM and $[Ca^{2+}]_i$ was measured by dual excitation microspectrofluorimetry. Depolarisation of the cell with KCl to a final concentration of 5 to 20 mM resulted in a rise in the $[Ca^{2+}]_i$ that rose to a peak and fell in a exponential fashion. Addition of isoprenaline (1 μM) during the phase of decline in $[Ca^{2+}]_i$ led to a further decrease in 11 cells studied. ($[Ca^{2+}]_i$ in nM (SEM): baseline, 124·1 (20·2); peak after KCl, 287·5 (42·5): before addition of isoprenaline 202·0 (27·5): after isoprenaline 167·9 (28·8) (p < 0·05). By contrast, the addition of CGRP (1 uM) resulted in a rise in $[Ca^{2+}]_i$ ($[Ca^{2+}]_i$ in nM (SEM): baseline, 175·3 (41·8); peak after KCl, 608·1 (145·3); before addition of CGRP, 302·8 (81·5); after CGRP 473·5 (90·7) (p < 0·001)). The p values represent *t* tests for $[Ca^{2+}]_i$ before and after isoprenaline or CGRP.

Although both receptor complexes are linked to the cyclic adenosine nucleophosphate system, isoprenaline and CGRP have differing effects on $[Ca^{2+}]_i$ handling in depolarised, calcium overloaded myocytes.

QT dynamics in patients with left ventricular hypertrophy and heart failure

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In patients with heart failure, ventricular arrhythmias may be more common at lower (near normal) heart rates. The QT interval, which alters with heart rate, reflects cellular processes that in turn may be important in arrhythmogenesis. We have therefore investigated the rate dependence of the QT interval in 25 patients with stable congestive heart failure (CHF), 12 patients with left ventricular hypertophy (LVH) and normal systolic function, and seven control subjects. In all subjects QRS duration was normal and none showed evidence of inducible ischaemia. Patient characteristics were: CHF, left ventricular ejection fraction (LVEF) mean (SEM) 29 (4)%, LV wall thickness 1·1 (0·1) cm; LVH, LVEF 58 (8)%, LV wall thickness 1·3 (0·1) cm; controls, LVEF 61 (2)%, LV wall thickness 0·9 (0·1) cm. Twenty-four hour electrocardiographic recordings were obtained within two weeks of the exercise test. On the study day autonomic tests for baroreflex sensitivity, standard deviation of 128 RR intervals, and venous catecholamine concentrations were measured with the subject lying supine. Subjects were then exercised to exhaustion on an upright bicycle ergometer in four minute, 25 watt stages. A 12 lead electrocardiographic record was taken every minute at 50 mm/s, 20 mm/mV. QT Interval was measured in standard lead II during the last 90 s of each stage. Resting heart rate was 72 (4) beats/min in controls, 66 (4) beats/min in LVH, 83 (4) beats/min in CHF (p < 0·01, unpaired *t* test, for failure *v* control or LVH). Resting QT interval was 389 (9) ms in controls, 403 (11) ms in LVH, 414 (15) ms in CHF. Bazett's formula corrects these values to 424 (10) ms in controls, 420 (6) ms in LVH, 481 (14) ms in CHF (p < 0·01 for CHF *v* control or LVH). Peak heart rate was 127 (8) in controls, 133 (7) in LVH, and 127 (5) in CHF, with QT values of 305 (8), 294 (12), and 316 (12) respectively. The steady state QT/heart rate slope, measured using least squares linear regression, was 1·62 (0·09), 1·67 (0·13), and 2·38 (0·16) ms/beats/min respectively (p < 0·01 for CHF *v* either hypertrophy or failure). Autonomic abnormalities and 24 hour tape findings did not relate to the degree of resting QT interval prolongation or to the increase in QT/heart rate slope steepness.

In heart failure QT interval is increased at rest and decreases more rapidly on exercise. As neither the degree of QT prolongation nor the QT/heart rate slope correlated with autonomic function, we suggest that these abnormalities are secondary to intrinsic changes in the cardiac myocytes in heart failure.

Heart rate and sympathetic contribution to exercise induced QT shortening

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Shortening of QT interval on exercise is related to heart rate and increased sympathetic activity, though the contribution of each is unknown. The relative contributions of heart rate and overall sympathetic activity in patients with dual chamber pacemakers implanted for sino-atrial node disease was investigated. Eight patients were exercised for 10 minutes on a bicycle ergometer at a steady workload to increase their heart rate to approximately 110 beats/min. After a two hour recovery period, they were paced while at rest on the bicycle to the same heart rate. QT intervals and forearm venous noradrenaline were measured at rest, during pacing, and during exercise, all at steady state. Mean heart rate (HR) at rest was 66 (2), on exercise was 112 (3), and on pacing was 107 (4) NS for HR_{pace} *v* $HR_{exercise}$). Uncorrected QT intervals were: QT_{rest} 420 (12) ms, QT_{pace} 366 (16) ms, and $QT_{exercise}$ 325 (14) ms (p < 0·005 for

$QT_{exercise}$ *v* QT_{pace}). Using linear correction for heart rate, the paced QT interval at the exercise heart rate was 359 (17) ms (p < 0·02 $QT_{exercise}$ *v* QT_{pace}). Thus the heart rate contribution to QT shortening was 69 (9)% of total QT shortening. Forearm venous noradrenaline concentration was 543 (94) pmol/l at rest, 571 (99) pmol/l during pacing and 1517 (282) pmol/l at 10 minutes exercise (p < 0·005 for exercise *v* rest). There was little correlation between the exercise induced component of QT shortening and the absolute or relative increase in noradrenaline concentration.

Two thirds of QT shortening on exercise is due to the increase in heart rate: the remaining one third is not closely related to forearm venous noradrenaline.

A novel approach to preoperative prediction of the outcome of coronary revascularisation by positron emission tomography (PET)

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Previous assessment of myocardial viability using positron emission tomography imaging relied on uptake of the glucose analogue, ^{18}F-fluorodeoxyglucose (FDG), in hypoperfused asynergic myocardium. A new method that enables simultaneous assessment of myocardial blood flow and tissue viability by positron emission tomography was developed. This relies on the calculation of the perfusable tissue index (PTI) from analysis of transmission, ^{15}O labelled carbon monoxide ($C^{15}O$, blood volume), and ^{15}O water ($H_2{}^{15}O$) emission data sets. The PTI is defined as the proportion of the myocardium that is perfusable by water and thus represents an index of tissue viability. In this study, preoperative assessment of myocardial viability using PTI was performed in 12 patients undergoing coronary revascularisation. In eight patients, an additional FDG scan was performed after a 75 g oral glucose load. Echocardiography performed three to six days before revascularisation identified 33 segments with abnormal wall motion and 26 control segments. Follow up echocardiography performed three to five months later showed 26/33 segments with improved wall motion (recovery) and 7/33 segments that did not recover (non-recovery). Myocardial blood flow in control regions was 0·97 (0·33) ml/min/g compared with 0·73 (0·18) ml/min/g in the recovery (p < 0·001 *v* control) and 0·45 (0·11) ml/min/g in the non-recovery (p < 0·001 *v* control) groups. The PTI in the recovery group was > 0·7 in all cases and was slightly less than in the control regions (0·99 (0·15) *v* 1·10 (0·15), p < 0·02). Uptake of FDG in these segments was 92 (17)% (n = 13) of the control value. In the non-recovery group, PTI was 0·62 (0·06) (p < 0·02 *v* control) and always < 0·7. This was associated with significantly reduced uptake of FDG in the one case where PTI and FDG were compared. This study shows the concordance between the PTI and FDG techniques and suggests that at least 70% of the myocardium should be perfusable by water (PTI > 0·7) to enable contractile recovery.

Our preliminary findings show PTI to be a good predictor of contractile recovery and suggest that myocardial viability may be assessed without metabolic imaging.

Measurement of myocardial perfusion in humans by ultrafast *x* ray computed tomography: validation by comparison with adenosine thallium tomography

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Ultrafast computerised tomography can be used to evaluate myocardial perfusion in dogs by applying first pass distribution indicator dilution principles. The technique has not previously been validated in humans. Seventy nine myocardial segments from five patients (all male, age 38 to 79) with coronary artery disease documented by angiography or myocardial infarction, or both were investigated. Myocardial perfusion at rest and during infusion of adenosine was assessed using thallium-201 single photon emission computed tomography and ultrafast computed *x* ray tomography. The ultrafast computed tomography scanner was set to acquire 6 mm thick tomograms in a single plane aligned roughly in the short axis of the left ventricle, with an exposure time of 100 ms. Radiographic contrast was delivered by mechanical injector into the superior vena cava and 20 images gated to end diastole were timed to acquire a baseline image followed by a series to allow the measurement of myocardial enhancement. The sequence was repeated 3 min after the start of intravenous adenosine infusion (140 μg/kg/min). Both thallium and ultrafast computed tomography short axis tomograms were divided into eight segments and the percentage variation of each segment from the mean flow tomogram or scintillation count (thallium) was calculated to give the segmental flow index. The flow indices of the 79 segments measured by the two techniques correlated (r = 0·7, slope = 1·2 intercept = −0·2, p < 0·05), the mean difference between the methods was 0·0075 with 95% confidence interval = 0·42. Using the thallium scan to define normal or abnormal flow in a segment, ultrafast computerised tomography agreed in 72 of 79 segments with a sensitivity of detection of abnormally reduced flow of 94% and a specificity of 79% (kappa statistic, $\kappa = 0{\cdot}7$ indicating good agreement overall).

These data show that ultrafast computerised tomography can be used to assess relative myocardial perfusion in humans, after intravenous administration of radiographic contrast.

Emergency surgical revascularisation performed within 24 hours of failed coronary angioplasty

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Between January 1980 and December 1990, 75 of 1539 patients (4·9%) required emergency surgical revascularisation within 24 hours of elective coronary angioplasty in a single centre with surgical facilities on site. In these cases, emergency surgery was undertaken for clinical deterioration: patients who underwent surgery within 24 hours for simple failure of angioplasty were excluded. After 1983, an operating theatre was not maintained on standby. Of the patients requiring emergency surgery, 57 (76%) were men, mean age 55 (range 29 to 73) and 30 (40%) had had a previous myocardial infarction. Before angioplasty, 68 (89%) were CCS grade III/IV, 59 (79%) had multivessel disease, and six (8%) had a left ventricular ejection fraction of less than 40%. A mean of 2·1 grafts (range one to five) were performed: the internal mammary was used in only one patient. The operative mortality was 9% and in hospital mortality was 17%. Crash bypass, (the requirement for cardiac massage until bypass was established), was necessary in 19 patients (25%): this was the most important outcome determinant and was more common in those patients with multivessel disease and in women. In 10 of these cases, a vacant operating theatre was unavailable: operation was performed in the catheter or anaesthetic room. Crash bypass patients had an operative mortality of 32% and in hospital mortality of 47%, compared with 2% and 7% respectively for the 56 remaining patients who awaited the next available operating theatre. Postoperative complications included arrhythmias (10), wound (five), renal (four), cerebral (two), and septicemia (two): major complications were invariably fatal in those requiring crash bypass. In survivors, mean time to discharge was similar in both groups (13 days, range 5 to 40 days).

The mortality and morbidity associated with emergency revascularisation is high compared with elective surgery: an 83% survival rate was achieved overall. Fifty three per cent of patients needing immediate crash bypass survived due to the availability of surgical backup on site.

Is the ventilation/perfusion mismatch which contributes to exertional hyperpnoea in chronic heart failure (CHF) dependent on limiting right ventricular (RV) output?

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In chronic heart failure, slope *m* of the exercise relation of minute ventilation/CO_2 production (V_EVco_2) is increased when exercise capacity is reduced to peak oxygen consumption (Vo_{2max}) <20 ml/min/kg, with peak Vco_2/Vo_2 (RER_{max}) > 1. We investigated whether the ventilation/perfusion (V/Q) mismatch underlying increased *m* might be attributable to limitation of right ventricular output and total pulmonary perfusion. In study I, of 42 patients (31 men, age 60 (SD8), drugs withdrawn) with coronary artery disease, positive exercise test, and angiographically normal resting left ventricular function, the 12 patients with exercise tolerance reduced to $Vo_{2max} < 20$ ml/min/kg and $RER_{max} > 1$ had the same *m* as 30 patients with $Vo_{2max} > 20$ ml/min/kg and 15 normal people (29 (5), 30 (6), 26 (5). Thus *m* was not increased where, by inference, the exercise induced increase in left ventricular (and thus right ventricular) output was impaired acutely. In study II the exercise induced increase in cardiac output was altered acutely in 13 pacemaker dependent patients by setting the pacemaker (in random order) at 50 beats/min fixed rate (VVI) or in rate-responsive mode (RRM) (which increased exercise heart rate by 51 (7) beats/min). Seven patients (group A) had normal resting left ventricular function (ejection fraction >50%); six patients (group B) had resting left ventricular dysfunction of mixed aetiology (ejection fraction <40%). Exercise duration and Vo_{2max} were lower during VVI than RRM in both groups (group A: Vo_{2max} 16·9 (0·9) *v* 20·1 (1·5) ml/min/kg ($p < 0{\cdot}05$); group B: 13·1 (2·3) *v* 16·1 (3·4) ml/min/kg ($p < 0{\cdot}05$). Abolishing the exertional increase in heart rate during VVI did not alter *m* in group A (31 (2) to 32 (1)) but increased *m* in group B (39 (5) to 51 (7) ($p < 0{\cdot}05$)); thus *m* can be acutely altered in chronic heart failure.

V/Q mismatch underlying the ventilatory response to exercise may reflect limitation of right ventricular output but only where resting left ventricular function is impaired, as in chronic heart failure.

Cardiac catheterisation in a consecutive series of young patients with first myocardial infarction: should all patients be investigated?

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After myocardial infarction, there is no established policy of who should undergo angiography. We have performed a study to see if postinfarction agina, or abnormal treadmill exercise, or both allows for appropriate decision making. A consecutive series of 186 patients (143 men) under 60 who were discharged from the coronary care unit with a first acute myocardial infarction (standard World Health Organisation criteria) were electively readmitted at a mean (SD) of 60 (31) days for symptom limited exercise testing (Bruce protocol) and cardiac catheterisation. Angina was assessed with a Rose questionnaire; 135 received thrombolysis. A further five patients died unexpectedly before investigation. Significant coronary artery disease was defined as stenosis of one of the three main coronary arteries of >50%. An exercise test was positive if >1 mm ST depression occurred at 80 ms past the J point, and negative without ST depression if >85% of the target heart rate had been achieved. Cine angiograms and exercise tests were reviewed independently by two observers and disagreements settled by a third. Follow up was to death, angioplasty, or bypass surgery. Single vessel disease or normal coronary arteries were present in 97, two or three vessel disease in 83, and left main stem disease in six. The sensitivity and specificity of exercise testing for detecting multivessel disease were 52% and 79% respectively. Of 50% patients with a negative exercise test and no angina only two had three vessel disease, 14 had two vessel disease and 34 had single or no significant disease. None of these 50 was referred for intervention, and none has died over a mean (SD) follow up of 12 (4) months. Of the six patients with left main stem disease all had exercise test times over six minutes and five had positive exercise tests; the sixth had left bundle branch block.

The young patient with a first myocardial infarction who does not have angina and who has a negative exercise test does not require cardiac catheterisation.

Exercise tolerance in angina is improved by Mivazerol (an α_2 adrenoceptor agonist)

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Many patients with chronic stable angina remain symptomatic despite maximal medical treatment or are unable to tolerate one or more of the triumvirate of β-blockers, calcium antagonists, and nitrates. Mivazerol is a new compound with agonist properties at the α_2 adrenoceptor and has been shown to be an effective antianginal drug in humans when given intravenously. This is the first report of its benefit in an orally administered form. Twelve patients with chronic stable angina and angiographically proved coronary heart disease entered a double blind, placebo controlled, randomised crossover study. Regular antianginal medication was withdrawn for 96 hours, and three ascending doses of mivazerol were compared with placebo using a standard Bruce protocol. All doses of mivazerol increased the total exercise duration, the time to onset of angina, and the time taken to develop 1 mm of ST segment depression. In order of increasing dose (800, 1200, 1600 μg) the improvement in exercise duration was 11% (p < 0·05), 20% (p < 0·05), and 24% (p < 0·01), in the time to onset of angina 3% (NS), 11% (0·05), and 30% (p < 0·01), and in the time to 1 mm ST depression 33% (p < 0·05), 43% (p < 0·01), and 53% (p < 0·01). The heart rate at peak exercise tended to be lower by 3%, 4%, and 3% (all NS). The systolic blood pressure attained at maximal exercise was lower by 11% (p < 0·01), 15% (p < 0·01), and 14% (p < 0·01) respectively.

Mivazerol significantly improved total treadmill exercise duration, the time to onset of angina, and the time to 1 mm ST depression in patients with chronic stable angina. This was associated with an attenuated rise in systolic blood pressure. Mivazerol is an α_2 adrenoceptor agonist and its mechanism of action may be different from that of the classic antianginal drugs.

Are 50% of hypercholesterolaemic patients receiving lipid lowering drug therapy unnecessarily?

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We initiated a trial of lipid lowering drug treatment for hypercholesterolaemia. The present study investigates an unexpectedly high (50%) dropout rate during the dietary stabilisation phase of the trial. Twenty men and women with primary hypercholesterolaemia were entered into the dietary stabilisation phase. All had received dietary advice before the study and were considered to be on a low cholesterol diet. Over three months they were seen four times by the dietician and again advised on diet. This advice was reinforced if patients showed poor compliance as judged by the food record rating scoring system. Patients completed a diary card aiming to score less than 15, thereby ensuring active patient participation. Plasma lipids were measured at the beginning and end of the dietary phase. Ten patients progressed into the active drug treatment phase with persistently raised cholesterol, 10 were withdrawn because of a mean fall in plasma cholesterol concentration from 7·91 mmol/l (range 6·90 to 9·86) to 5·74 mmol/l (range 4·60 to 6·40), p < 0·001. Despite previous advice, in 50% of our population cholesterol concentrations fell to near normal with more disciplined supervision.

We believe that dietary treatment in the United Kingdom is inadequately supervised. Lipid lowering drugs are given without a thorough trial of diet with obvious cost implications and unnecessary drug prescription.

Release and metabolism of the novel cardiac hormone, brain natriuretic peptide, in humans

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Brain natriuretic peptide (BNP) was first isolated from the porcine brain. Subsequent studies have shown that BNP is a cardiac hormone synthesised and secreted in the heart and constitutes, together with atrial natriuretic peptide (ANP), a natriuretic peptide family involved in cardiovascular homeostasis. We have recently conducted four studies examining the release and metabolism of BNP in humans. In the first study, we examined the effect of changes in salt intake on plasma BNP concentrations in healthy volunteers (n = 11, age 20 to 23). Plasma BNP concentration (mean (SE)) rose significantly on high salt intake, from 1·3 (0·2) pmol/l to 2·0 (0·1) pmol/l (p < 0·05). To elucidate further the release of BNP in humans, we examined the effect of fluid removal by haemodialysis on plasma BNP concentrations in volume overloaded dialysis dependent patients with chronic renal failure (n = 10, age 16 to 73). The fall in plasma BNP concentration from 21·0 (3·8) pmol/l to 18·1 (3·2) pmol/l correlated strongly with weight reduction after haemodialysis (r^2 = 0·64, p < 0·01). The last two studies examined BNP clearance in congestive heart failure patients (n = 7) who have raised plasma BNP concentrations. 200 mg Candoxatril, an endopeptidase 24·11 inhibitor, increased plasma BNP concentrations from 15·2 (4·4) pmol/l to 24·4 (7·4) pmol/l (p < 0·05). Infusion of a large dose of ANP, however, which saturates the ANP clearance receptors did not alter BNP concentrations.

Like ANP, BNP is sensitive to changes in salt and volume in humans. In congestive heart failure patients there is a role for neutral endopeptidase but not for ANP clearance receptors in the metabolism of BNP.

Effects of hormone replacement on lipid and lipoprotein cardiovascular risk markers in postmenopausal women

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Hormone replacement therapy results in a pronounced decrease in incidence of cardiovascular disease in postmenopausal women. Current hormone replacement therapy regimens combine a progestin with oestrogen. To study the effects of hormone replacement therapy on serum lipids and lipoproteins, we randomly allocated 60 healthy postmenopausal women to either oral (continuous conjugated equine oestrogens (0·625 mg daily) with sequential dl norgestrel (0·15 mg daily)) or transdermal (continuous oestradiol-17β (0·05 mg daily)) with sequential norethisterone acetate (0·25 mg daily) hormone replacement therapy. An untreated reference group of 29 women were recruited concurrently. Fasting blood samples were taken basally, at three and six months, and at six monthly intervals thereafter throughout the three year study. Compliance was monitored by recording bleeding patterns and by serum gonadotrophin and gonadal steroid measurements.

Changes in lipids and lipoproteins were seen at three months, and were maximal by six months. These changes persisted throughout the three years. In both treatment groups, we found a significant decline in total cholesterol and low density lipoprotein cholesterol concentrations. These changes were accompanied by similar changes in concentrations of apolipoprotein B. Concentrations of high density lipoprotein cholesterol and apolipoprotein AI also declined in the combined phase of treatment, due to a decrease in high density lipoprotein subfraction 3. No consistent pattern of change in concentrations of high density lipoprotein subfraction 2 was found with either treatment. Triglyceride concentrations were raised during the oestrogen alone phase of oral treatment, but were reduced during this phase of the transdermal treatment. Addition of progestin lowered triglycerides with both treatments.

Hormone replacement therapy brings about beneficial changes in lipids and lipoproteins irrespective of the route of administration. Such changes may in part explain the reduction in incidence of coronary artery disease in postmenopausal users of hormone replacement therapy.

Intense inhibition of angiotensin converting enzyme (ACE) enhances frusemide induced diuresis during chronic ACE inhibitor therapy

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Short-term angiotensin converting enzyme (ACE) inhibition in heart failure reduces the diuretic response to frusemide. The interaction of diuretics and ACE inhibitors long-term has not been studied. Seven patients with heart failure treated with diuretics (mean dose 91 mg frusemide) and ACE inhibitors (captopril (12·5 mg three times daily) for at least three months were studied. Sodium intake was fixed for three days before study. Usual medication was withheld on study days. Frusemide was given by hourly bolus in identical fashion on each of two study days (mean total for the four hours was 15 mg) to maintain a moderate constant diuresis. Para amino hippurate and inulin were infused to calculate renal plasma flow and glomerular filtration rate (GFR). The patient was asked to void urine hourly for four hours. Captopril (12·5 mg) or matching placebo was given in random order 10 minutes before the end of the first urine collection. Plasma electrolytes and angiotensin II (A-II) were measured hourly. Captopril reduced plasma A-II one hour after dosing. Urine volume increased following captopril, most noticeably in the second hour after dosing (240 (83) to 313 (99) ml/hour; $p < 0·01$). Systolic blood pressure fell (131 (31) to 122 (29) mm Hg; $p < 0·01$) and diastolic blood pressure likewise (74 (15) to 67 (13) mm Hg; $p < 0·01$) but heart rate and GFR were unchanged two hours after the dose. Urinary electrolyte concentrations fell after captopril suggesting increased free water clearance, but urinary sodium excretion (22 (7) to 29 (12) mmol/h; $p < 0·01$) and sodium:creatinine ratio, a measure of fractional excretion of sodium (64 (27) to 77 (36) mmol/μmol; $p < 0·01$) increased. The ratio of sodium to phosphate, potassium, and magnesium excretion all increased suggesting that neither proximal nor distal tubular effects accounted for the increase in sodium excretion.

Intensive treatment with ACE inhibitors to maximally suppress A-11 formation enhances the natriuretic and aquaretic response to frusemide.

Selective inhibitors of protein kinase C are potent inhibitors of vascular smooth muscle proliferation

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Inhibition of vascular smooth muscle cell proliferation is a possible therapeutic strategy for angioplasty restenosis, vein graft occlusion, and atherosclerosis. As vascular smooth muscle cell proliferation may require activation of protein kinase C, we investigated the effects of inhibitors of protein C on proliferation. We studied the novel staurosporine derivatives Ro 31-8220 and Ro 31-7549, which show 100 fold selectivity for protein kinase C over other protein kinases. Proliferation of first passage rabbit aortic smooth muscle cells was quantified by incorporation of thymidine into DNA and cell viability by measurements of ATP concentration. Cells were rendered quiescent by culture for 72 hours in serum free medium and then stimulated with medium containing 1 μCi/ml of ^{3}H-thymidine and (*a*) 5% fetal calf serum, (*b*) a combination of 10 μM serotonin and 20 ng/ml of platelet derived growth factor (recombinant BB dimer), or (*c*) 0·1 μM of the protein kinase C activator, phorbol dibutyrate, which stimulated proliferation by (mean (SE) (n)) 65 (14) (7), 5 (1) (4), 4 (1) (4) respectively (all $p < 0·001$). Proliferation to the three stimuli was inhibited by 10 μM Ro 31-8220 to 0·5 (0·2) (7), 9 (4) (2), and 5 (1) (4)% respectively, of proliferation rates in the absence of inhibitor (all $p < 0·001$), without any effect on cell viability measured by ATP concentration (110 (2), 120 (10), and 110 (20)% of values in the absence of inhibitor, all NS). Similar effects on proliferation were obtained with 10 μM Ro 31-7549 (data not given). The concentrations of Ro 31-8220 and Ro 31-7549 that gave 50% inhibition of proliferation to serum (1·7 (0·4) (3) μM and 5 (1) (3) μM) were similar, although slightly higher, than those to phorbol dibutyrate (0·7 (0·1) (2) μM and 1·1 (0·5) (2) μM).

The data show that Ro 31-8220 and Ro 31-7549 are highly potent inhibitors of vascular smooth muscle cell. They imply, furthermore, that protein Kinase C activation is essential for proliferation responses to serum and serotonin plus platelet derived growth factor.

A comparative study of risk factors for coronary artery disease in south Asian and white people

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Diffuse coronary artery disease (CAD) is a striking cause of mortality and morbidity amongst immigrants from the Indian subcontinent (south Asians). In a case control study we investigated 228 men, mean age (range) 54 (34 to 68). Patients (62 Asian and 52 white people) were studied at least six months after any acute event and had angiographically documented coronary artery disease or electrocardiographic evidence of myocardial infarction. The age matched controls (62 Asian and 52 white) were selected randomly from the patients' general practitioner lists. There was a significant Asian *v* white difference for mean values of insulin (18·6 *v* 12·2 iu/l, $p < 0·001$) and cholesterol concentrations (5·32 *v* 5·87 mmol/l $p = 0·001$); platelet volume (9·16 *v* 8·81 fl p = 0·008); white blood cell count (7·78 *v* 6·96 × 10^9/l, p = 0·002); occlusion stimulated fibrinolytic activity (101 *v* 137 mm, p < 0·001); systolic blood pressure (120 *v* 130 mm Hg, p < 0·001), and diastolic blood pressure (78 *v* 82 mm Hg, p = 0·007). There was a significant patient *v* control difference in mean values for insulin (18·2 *v* 13·9 iu/l, p = 0·013); cholesterol (6·01 *v* 5·25 mmol/l, p < 0·001); triglyceride (3·11 *v* 1·98 mmol/l, p = 0·001); ApoB100 (83·2 *v* 75·3 mg/dl, p < 0·001); ApoA1 (117·0 *v* 128·6 mg/dl, p < 0·001); and Lp (a) concentrations (30·9 *v* 7·4 mg/dl, p < 0·001); body mass index (26·1 *v* 25·1, p = 0·036); body fat (22·1 *v* 20·7%, p = 0·029); and fibrinogen (2·29 *v* 2·11 g/l, p = 0·032); factor VII (135 *v* 167%, p = 0·014); platelet (274 *v* 238 × 10^9/l, p = 0·001); β-thromboglobulin (48·7 *v* 30·4 iu/ml, p < 0·001), and platelet factor 4 (12·1 *v* 5·8 iu/ml, p < 0·001) concentrations. A history of diabetes was more common in south Asians than in white people (21% *v* 6%) and reported hypertension more common among white people (25% *v* 35%). Smoking habits were roughly equal (87% *v* 89%). In south Asians a metabolic state of hyperinsulinaemia and diabetes mellitus may be responsible for their high incidence of coronary artery disease, but the decreased fibrinolytic capacity, the higher white blood cell count and the larger platelets may also be important contributory factors.

Whereas this study can only consider survivors, it is likely that these factors will also be risk factors for coronary artery disease.

Insulin, alcohol, and the risk of cardiovascular disease in middle aged men

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Because the mechanisms underlying the alcohol cardiovascular disease relation are unclear, we studied the relation between alcohol consumption and fasting plasma insulin and lipoprotein concentrations in a stratified random sample of 824 men aged 40 to 69 who attended a health survey in east Bristol. Light to moderate drinkers (>5–40 g alcohol/day), compared with non or occasional drinkers (0–5 g alcohol/day), had lower plasma insulin concentration by 13% or 1·0 mU/l, lower cholesterol concentration by 4% or 0·2 mmol/l, and lower total cholesterol: HDL cholesterol ratio by 7% or 0·4, but higher total high density lipoprotein cholesterol concentration by 7% or 0·08 mmol/l and higher high density lipoprotein$_3$ cholesterol concentration by 8% or 0·06 mmol/l. Conversely, heavy drinkers (>40 g/day) compared with light to moderate drinkers, had higher plasma insulin concentration by 19% or 1·3 mU/l and higher total high density lipoprotein cholesterol concentration by 11% or 0·13 mmol/l but lower total cholesterol: high density lipoprotein cholesterol ratio by 8% or 0·4. All these differences were statistically significant and were shown to be independent of body mass index and smoking habits by multiple regression analysis and one way analysis of variance (Ancover).

The U shaped relation between plasma insulin and alcohol consumption might explain some of the decrease in coronary heart disease among moderate drinkers and the increase in hypertension among heavy drinkers.

Linoleic acid and the risk of sudden cardiac death

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An inverse relation between the essential fatty acid linoleic acid and the risk of angina pectoris and acute myocardial infarction in men has already been shown. We therefore investigated in a population case control study whether linoleic acid was related to the risk of coronary heart disease presenting as sudden cardiac death. The relative amount of linoleic acid was measured in adipose tissue as a marker of long term dietary intake of this fatty acid. Sixty five cases of sudden cardiac death occurring in men under the age of 65 with no history of coronary heart disease were identified from the City of Southampton. Subcutaneous adipose tissue was sampled from the abdomen at post mortem and stored at −70°C. Two hundred and thirty six living healthy age and sex matched controls, with no history of coronary heart disease, were drawn from general practices in which sudden cardiac death cases were registered, and a needle biopsy of adipose tissue was sampled from the same site under local anaesthetic and stored in the same way. The proportionate storage of linoleic acid in adipose tissue was measured by gas liquid chromatography with the laboratory blind to the state of adipose tissue samples.

The estimated relative risk of sudden cardiac death was 4·6 (95% confidence interval 1·61–13·1) when comparing the lowest quintile of adipose tissue:linoleic acid distribution in the controls with the top quintile. This inverse relation between linoleic acid and risk of sudden cardiac death is further evidence that a lower intake of this essential fatty acid increases the risk of coronary heart disease.

Assessment of the prevalence of coronary heart disease (CHD) in south Asians: difficulties with conventional methods

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A random population survey was carried out to detect the presence of coronary heart disease in south Asians who form 85% of the residents in a ward of Southall. A total of 375 patients (193 men and 182 women) age range 30 to 64 participated. A history of angina and myocardial infarction was obtained, and the Rose questionnaire was administered by an interviewer who spoke the patient's language. A cardiologist also obtained an independent history. The resting electrocardiogram was analysed using the Minnesota code for Q/QS patterns, and for ischaemia according to criteria specified in the Whitehall Study. Angina was detected by history in 2·6% men and 2·2% women, by Rose questionnaire in 4·7% men and 4·9% women, and by a cardiologist in 4·1% men and 0·6% women. A history of myocardial infarction was detected by history in 4·1% men and no women, by Rose questionnaire in 5·2% men and 2·2% women and by a cardiologist in 4·1% men and 0·5% women. Q/QS codes were present in 1·6% men and 0·6% women whereas 12·4% men and 13·7% women satisified the criteria for ischaemia. In men there was significant correlation between history and cardiologist for a diagnosis of myocardial infarction ($p < 0.001$), and borderline significance for a diagnosis of angina ($p = 0.07$), but no significant correlations for myocardial infarction or angina between the Rose questionnaire and history or cardiologist. There were no correlations in women for myocardial infarction or angina between Rose questionnaire, history, and cardiologist. The rates of Q/QS codes were similar to known values for the British population (Whitehall and Scottish Heart studies) whereas ischaemic electrocardiographic abnormalities had higher rates in both south Asian men and women. Such abnormalities occurred in predominantly asymptomatic persons. These findings suggest that the administered Rose questionnaire, originally validated in white men, needs to be used with caution in south Asians, and especially women when assessing prevalence of coronary heart disease.

If ischaemic electrographic criteria based on ST-T abnormalities are to be used for assessment of prevalence of coronary heart disease in ethnic groups and particularly in women then further validation is necessary.

Prevalence of coronary heart disease in south Asians living in west London is not higher than in the English population

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Although standardised mortality ratios (SMRs) suggest a 36% higher mortality from coronary heart disease in south Asians living in London compared with the native population, there are no comparative data on the prevalence of coronary heart disease in south Asians. To determine the prevalence of overt coronary heart disease in south Asians, a random selection of case notes and appropriate hospital records of two general practices with a predominantly south Asian population were studied and compared with a third practice, within two miles of the others and serving a similar social group but predominantly English population. Patients who had documented myocardial infarction, positive coronary angiography, cardiac surgery, or cardiac chest pain (supported by investigations) were regarded as having overt coronary heart disease. The notes of 1510 south Asian 30 to 64 year old men were examined, giving 45 cases of overt coronary heart disease, a prevalence of 3·0% (95% CI 2·1–3·8). For 1176 English men of similar age 34 cases of overt coronary heart disease were identified, a prevalence of 2·9% (1·9–3·9). The prevalence within different age bands was as follows for Asians *v* English: 30–39, 0·9% (0·33–2·02) *v* 0·2% (0·01–1·35); 40 to 49, 1·7% (0·70–3·59) *v* 1·7% (0·62–3·69); 50 to 59, 6·1% (3·85–9·12) *v* 5·2% (3·25–9·34); 60 to 64, 10·1% (5·28–18·89) *v* 10·0% (5·28–16·86). Different Asian subpopulations showed different prevalence rates—namely, Moslem 4·7% (3·13–6·63), Sikh 2·0% (1·03–3·48) ($p = 0.008$).

These data show that (*a*) the prevalence of overt coronary heart disease appears low in south Asians and is similar to that of the English. (*b*) Differences exist within Asian subpopulations.

Factors influencing the use of thrombolytic therapy in six district general hospitals

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A prospective audit of time delays in the admission of patients with acute myocardial infarction (AMI) and the utilisation of thrombolysis was performed in six district hospitals. Of 1746 patients admitted with possible AMI, and for whom accurate timing of the onset of symptoms is available, 1341 (77%) arrived at hospital within six hours. Further arrivals over the next six hours increased the total to 1560 (89%), an hourly increment of only 2%. Of 1069 patients with a final diagnosis of definite AMI, 44% received thrombolysis within six hours of onset of symptoms and 59% within 24 hours. A contraindication was stated in 398 (37%), whereas 43 (4%) had no stated contraindication to thrombolysis nor did they receive it. Most contraindications, based on a final diagnosis of AMI, fell into four groups: diagnosis uncertain 73/398 (18·3%); non-qualifying electrocardiogram 81/398 (20·3%); too late 79/398 (19·8%), and other 89/398 (22·4%). "Other" was a contraindication that required an explanation on the data entry form; in only 4/89 was an explanation provided. "Too late" was a locally determined criterion influenced partly by participation in trials of late thrombolysis. The frequency of use of contraindications varies widely between hospitals (25–47%). "Diagnosis uncertain" and "non-qualifying electrocardiogram" are to some degree subjective, and diagnostic uncertainty appears to be common. Of patients having an admission diagnosis other than definite AMI, that is, probable AMI, unstable angina, chest pain of uncertain cause, 410/1264 (32%, range 23–43%) had a final diagnosis of AMI. By contrast 28/670 (4%) with an admission diagnosis of AMI subsequently had the diagnosis changed. The use of thrombolysis depends on the admission diagnosis; 71% of patients with an admission diagnosis of definite AMI had thrombolysis, whereas 43% of those in whom the diagnosis was changed to one of definite AMI received thrombolysis. Although complete concordance between admission and final diagnosis is not realistic the variation between hospitals suggests that improvement in diagnostic accuracy may be possible.

A substantial reduction in prehospital delays, although desirable, will not greatly increase the total use of thrombolysis within the first six hours after onset of symptoms. The number of patients not receiving thrombolysis because of contraindications varies by a factor of two between hospitals; this may reflect diagnostic uncertainty. More rigorous use of contraindications could increase the use of thrombolysis within hospital.

Tricuspid annular dilatation: an important cause of tricuspid regurgitation after mitral valve replacement

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The development of late tricuspid regurgitation after mitral valve replacement is accompanied by a considerable reduction in exercise capacity and poor functional outcome. We have attempted to define its pathogenesis more clearly by comparing the clinical and echocardiographic characteristics of two groups of patients, with (n = 13) and without (n = 13) clinically significant tricuspid regurgitation after mitral valve replacement. The groups were matched for age and sex and were studied at similar intervals postoperatively (mean (SD) 8·5 (4·8) yr *v* 7·3 (2·8) yr; NS). The severity of preoperative symptoms was comparable but current functional state was worse in those with severe tricuspid regurgitation (New York Heart Association III or IV), 6/13 *v* 1/13; p < 0·01). Preoperative haemodynamic data were similar but mild tricuspid regurgitation was detected at preoperative palpation only in the group who later developed clinically significant tricuspid regurgitation (5/13 *v* 0/13 (p < 0·02)). Current echocardiographic parameters of left ventricular function were similar but right ventricular diameter was greater in those with severe tricuspid regurgitation (4·9 (0·4) cm *v* 4·0 (0·8) cm; p < 0·01). None of the patients had evidence of rheumatic tricuspid valve disease but the tricuspid annulus was wider in those with severe tricuspid regurgitation 3·7 (0·5) cm *v* 3·2 (0·4); p < 0·05). Prosthetic function was normal in all patients and estimated pulmonary artery systolic pressure was comparable in the two groups (38 (10) mm Hg *v* 30 (14) mm Hg; NS).

These results indicate that late tricuspid regurgitation after mitral valve replacement is related to tricuspid annular dilatation occurring in the absence of pulmonary hypertension. Its detection and correction at the time of initial surgery may lead to a reduction in the prevalence of this important complication of mitral valve replacement.

Effect of retrograde non-transseptal balloon dilatation of the mitral valve on left atrial function in mitral stenosis

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Retrograde non-transseptal balloon dilatation of the mitral valve (RNBMV) for mitral stenosis with a steerable cardiac catheter is a new, effective, and safe technique developed in our institute. It does not involve puncture of the atrial septum, thus being the only technique that allows reliable assessment of left atrial function. Of the 117 patients who underwent RNBMV for mitral stenosis 13 patients (age 48 (11) in sinus rhythm, before and six months after RNBMV were studied. Left atrial volumes (cm^3) were measured echocardiographically at mitral valve opening (maximal, V max), at onset of left atrial systole (P wave of the electrocardiogram, Vp), and at mitral valve closure (minimal, V min) from the apical (2) and (4) chamber views using the biplane area length method. Left atrial contractile function was assessed with the left atrial active emptying fraction (ACTEF) = (Vp–Vmin)/Vp. Mitral valve area (MVA, cm^2) was assessed with pulsed Doppler. After RNBMV: MVA (0·83 (0·31) *v* 1·96 (0·37), p < 0·0001) and ACTEF increased (0·23 (0·06) *v* 0·29 (0·09), p < 0·005), Vmax decreased (118 (24) vs 83 (14), p < 0·0001), and Vmax was inversely related to MVA (r = 0·81).

RNBMV for mitral stenosis reduces left atrial size and improves left atrial contractile function. Reduction of left atrial size is an important indicator of the effectiveness of RNBMV.

Does biplane transoesophageal imaging confer advantages in the assessment of mitral prosthesis function?

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To determine whether biplane transoesophageal (TEE) imaging offers any advantages in the evaluation of mitral prosthetic function when compared with either standard single transverse plane (T-TEE) imaging or the precordial (PE) approach, a series of 43 consecutive patients with suspected prosthetic dysfunction (eight bioprostheses; 35 mechanical) were studied. Clinical indications included suspected transvalve or paravalve leakage (32), endocarditis (five), source of emboli (three), acute valve obstruction (two), mitral annulus rupture (one patient). All had had an earlier PE study. Correlative surgical confirmation of the TEE finding was subsequently available in 15 patients, and catheterisation confirmation in 24/28 of the remainder. Only four patients, all with normal PE and TEE findings, did not undergo correlative studies. Two independent blinded observers reported both the PE and TEE studies comparing information gained from PE imaging, transverse plane TEE, longitudinal plane TEE, and by combining information from both TEE planes. Both PE and TEE suggested eight patients to have normal prosthesis function. In the remaining 35 patients (all with pathological prosthetic function), PE failed to detect the lesion in 28/35 cases. The following lesions were identified by biplane TEE; vegetations or infective sequelae (five), left atrial or prosthetic thrombus (three), acute prosthetic thrombosis (one), mitral annulus rupture with pseudoaneurysm formation (one), prosthetic obstruction due to sub valve pannus (one). In the remaining 25 patients, pathological mitral regurgitation was the only abnormal finding. This was defined by ultrasound criteria as mild (six), moderate (four), and severe (15). In 12 cases the leak was single and paravalvar, in six there were two major paravalvar leaks, in three there were three, in two it was central orifice and in one there was a combination of paravalvar and central orifice leakage. Biplane imaging proved to have many advantages over imaging in either single plane as only it allowed a complete scan of the valve sewing ring. The longitudinal plane (L-TEE) proved optimal for the identification of leaks (L-TEE 17; T-TEE 9) or other pathological lesions sited anteriorly or posteriorly on the valve or around the sewing ring whereas transverse plane was superior at detecting medial or lateral leaks (L-TEE 14; T-TEE 20) or pathology.

Thus imaging in both TEE planes is a prerequisite for a complete mitral prosthesis evaluation.

Magnetic resonance jet velocity mapping validated against Doppler echocardiography in mitral and aortic valve stenosis

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To evaluate the accuracy of magnetic resonance phase shift jet velocity mapping in vivo, we used a 0·5 tesla Picker magnetic resonance machine and a field even echo rephasing sequence with a very short (3·6 ms) echo time to measure peak poststenotic jet velocity in 15 consecutive patients recruited with known valve disease (five mitral stenosis, three of these restudied after balloon dilatation of the mitral valve, and 11 aortic stenosis). On the same day as the magnetic resonance study, these patients underwent Doppler echocardiographic measurement of peak jet velocity by an experienced investigator; both studies were performed blind. In addition, the results of 10 further magnetic resonance investigations of aortic stenosis in patients referred for magnetic resonance imaging were reviewed. In the 15 recruited patients, 18 out of 19 magnetic resonance studies produced velocity maps from which peak jet velocities could be measured, and results showed good agreement with those from Doppler measurement ($r = 0{\cdot}94$, mean = 3·1 m/s, range: 1·5 to 5·9 m/s, mean of differences = $-0{\cdot}23$ m/s, limits of agreement = 0·96 m/s). The poor quality of one velocity map was attributed to misplacement of the imaging slice. Satisfactory magnetic resonance velocity maps were obtained in all of the remaining 10 cases, in two of which, distortion and calcification of the valves rendered accurate Doppler assessment impracticable.

In vivo magnetic resonance peak jet velocity measurements agree well with those made by Doppler ultrasound. The technique is likely to have value for measurement of jet velocity at locations where ultrasonic access is limited.

Pharmacological increase of extracellular magnesium concentrations slows conduction in normal ventricular myocardium independently of stimulation frequency

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Experimental evidence suggests that magnesium salts protect against the development of malignant ventricular arrhythmias during acute myocardial ischaemia by effects on conduction velocity. Although it is now well established that pharmacological elevation of extra-cellular magnesium concentrations in humans has no influence on ventricular refractoriness, the changes in intraventricular conduction have not been formally assessed other than by measurement of paced QRS duration which has produced conflicting results. Accordingly, we studied the effect of intravenous magnesium salts on the conduction time between two right ventricular endocardial sites in eight patients (age 23 to 51) with structurally normal hearts undergoing intracardiac electrophysiological investigations. Signals from a standard multipolar electrode catheter in the right ventricular apex and a monophasic action potential contact electrode catheter in the right ventricular outflow tract were recorded continuously, digitised at 1 kHz and stored on optical disc for subsequent analysis. Constant rate pacing was performed via the multipolar catheter at 500 and 300 ms cycle lengths and the conduction time from the stimulus artefact to monophasic action potential upstroke of the contact electrode was measured before and after administration of intravenous $MgSO_4$ (0·2 mmol/kg). Serum Mg concentration rose from 0·87 (0·04) to 2·31 (0·35) mmol/l ($p < 0{\cdot}0001$). Paced QRS duration increased from 146 (16) to 152 (19) ms at the 500 ms cycle length ($p < 0{\cdot}05$) and from 142 (9) to 146 (10) ms at the 300 ms cycle length ($p = 0{\cdot}06$). The conduction time between the right ventricular sites was prolonged from 54 (11) to 60 (9) ms ($p < 0{\cdot}01$) and from 55 (11) to 62 (10) ms ($p < 0{\cdot}001$) at the 500 and 300 ms cycle lengths. There was no significant change in monophasic action potential duration at 50, 70, or 90% repolarisation at either cycle length or in ventricular effective refractory period.

Acute pharmacological increase in extracellular magnesium concentrations slows intraventricular conduction in normal myocardium. This effect seems to be independent of stimulation frequency and is unlikely to involve modulation of fast sodium channels.

Regional thallium-201 washout rate and myocardial hypertrophy in hypertrophic cardiomyopathy: relation to exertional chest pain

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To study the mechanism of exertional chest pain in hypertrophic cardiomyopathy (HCM), we performed dipyridamole loading thallium-201 single photon emission computed tomography in 82 consecutive patients with hypertrophic cardiomyopathy and analysed the three hour washout rate of thallium, in relation to the single photon emission computed tomography image, regional wall thickness on cross sectional echocardiography, and other clinical findings using uni- and multivariate analysis. Twenty five of 82 (31%) patients had a history of exertional chest pain and showed a significantly lower total washout rate and greater maximal left ventricular wall thickness than patients without chest pain (32·0 (10·0)% *v* 37·1 (9·3)%, $p = 0{\cdot}027$; 26·7 (7·4) mm *v* 22·8 (7·3) mm, $p = 0{\cdot}031$ respectively). Even in mild or non-hypertrophied areas, patients with chest pain had a significantly lower regional washout rate than patients without pain (32·5 (10·4)% *v* 38·0 (9·4)%, $p = 0{\cdot}022$) despite similar left ventricular wall thickness (11·5 (2·3) mm *v* 11·4 (2·7) mm, NS). There was a weak correlation of regional washout rate and regional wall thickness in 298 analysed quadrant areas ($r = -0{\cdot}29$, $p = 0{\cdot}0001$); the correlation was similar even in severely hypertrophied areas ($r = -0{\cdot}35$, $p = 0{\cdot}0015$). Discriminant analysis identified a reduced washout rate, greater maximal left ventricular wall thickness, and supraventricular arrhythmias as the best predictors of exertional chest pain (sensitivity 68%, specificity 64% and accuracy 67%: $p = 0{\cdot}009$).

These results suggest that exertional chest pain in hypertrophic cardiomyopathy relates to reduced coronary flow reserve, which is a function of the disease process, and not the magnitude of left ventricular hypertrophy.

Repolarisation abnormalities in patients with hypertrophic cardiomyopathy and ventricular arrhythmias: are they important?

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Patients with hypertrophic cardiomyopathy have a high incidence of ventricular arrhythmias. One possible mechanism for these arrhythmias is inhomogeneity of repolarisation secondary to the disorganisation of myocardial architecture seen in this condition. To investigate this mechanism, assessment of ventricular repolarisation was undertaken in 31 patients with hypertrophic cardiomyopathy (mean age 39, 20 men), 14 of whom had documented clinical or inducible ventricular arrhythmias, in an attempt to elucidate possible abnormalities of repolarisation that might provide a substrate for these arrhythmias. Patients with and without arrhythmias were similar in terms of clinical, echocardiographic, and basic electrophysiological features. QT and QTc dispersion was determined by measuring the QT interval and determining the QTc value in each of the 12 leads of a standard electrocardiograph that was enlarged by a factor of four. In addition, all patients underwent electrophysiological study including measurement of dispersion of endocardial monophasic action potential duration from right and left ventricles.

QT and QTc dispersion and monophasic action potential dispersion were also evaluated in a control group with no structural heart disease. QT and QTc dispersion was similar in patients with and without ventricular arrhythmias (QT dispersion 76 (40) ms *v* 64 (11) ms, QTc dispersion 0·08 (0·04) s *v* 0·07 (0·01) s), although overall QT and QTc dispersion were increased as compared with controls (43 (12) ms, $p = 0{\cdot}001$ and 0·05 (0·02) s, $p = 0{\cdot}002$ respectively). Monophasic action potential dispersion was increased in the patients with hypertrophic cardiomyopathy (63·6 (39) ms) as compared with controls (26 (5) ms, $p < 0{\cdot}05$), but again there was no difference in the degree of dispersion between those with and without ventricular arrhythmias.

This study has shown that abnormalities of ventricular repolarisation are present in patients with hypertrophic cardiomyopathy as measured by an increase in QT and QTc dispersion and an increase in monophasic action potential dispersion. This is not associated, however, with the presence of clinical or inducible ventricular arrhythmias. Thus dispersion of repolarisation does not appear to be relevant to the genesis of ventricular arrhythmias in this condition.

Phosphorus-31 magnetic resonance spectroscopy of the failing heart in ischaemic cardiomyopathy, myocarditis, and severe valve disease

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Heart failure is a recognised feature of diseases of the myocardium such as myocarditis, ischaemic cardiomyopathy, and severe aortic and mitral valve disease. Abnormalities in metabolism may underlie the development of decompensated failure and the metabolic changes may be the same regardless of the etiology of the disorder. To examine ATP and phosphate energetics 29 patients were compared with 13 controls using a 1·9 Tesla 60 cm bore magnet. The phase modulated rotating frame imaging technique was used for spectroscopy and cardiac spectra were localised using stacked plots. The phosphocreatine (PCr) and ATP peaks were triangulated and an adjustment for ATP contamination from blood was made. Eighteen patients with symptoms of heart failure (New York Heart Association II–III) and on treatment (fractional shortening 27(10)%; end diastolic dimension; 6·0 (1·0) cm; left ventricular end diastolic pressure, 16·0 (8·0) mm Hg) had a PCr:ATP ratio of 1·06 (0·38) that was significantly ($p < 0{\cdot}01$) lower than in controls (1·5 (0·2)) or in the 11 patients with no dyspnoea (fractional shortening, 41 (7·4)%; end diastolic dimension, 5·7 (1·2) cm; left ventricular end diastolic pressure, 11·0 (7·4) mm Hg); PCr:ATP, 1·63 (0·2).

Phorbol ester and adenosine triphosphate potentiate adenylate cyclase activity in endothelial cells

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Interaction between different intracellular second messenger systems ("crosstalk") may modulate the response of a cell to an extracellular stimulus. This phenomenon was investigated in cultured bovine aortic endothelial cells (BAEC). These were pretreated for 30 min in culture with 100 nM phorbol 12-myristate 13-acetate (PMA; an activator of protein kinase C, PKC), 50 μM adenosine triphosphate (ATP), or culture medium alone and were then washed and harvested. Basal activities, and forskolin (10 μM), sodium fluoride (NaF, 10 mM), and isoprenaline (10 μM) stimulated adenylate cyclase activities were measured in BAEC homogenates. Pretreatment with PMA increased basal and stimulated adenylate cyclase activity above control values in a dose dependent manner: basal mean (SEM) 16·8 (1·6) *v* 12·2 (1·2), forskolin 116·0 (9·7) *v* 79·8 (6·0), NaF 104·7 (7·5) *v* 72·2 (5·0), isoprenaline 41·3 (3·3 *v* 34·1 (2·4) pmol cyclic AMP/min/mg protein, $p < 0{\cdot}01$ for all, $n = 14$. Pretreatment with ATP had a similar effect on adenylate cyclase activity: basal 21·5 (5·7) *v* 19·1 (5·7), forskolin 79·5 (11·4) *v* 62·4 (4·6), NaF 93·3 (17·2) *v* 73·3 (14·2), and isoprenaline 57·8 (8·6) *v* 43·7 (7·0) pmol cyclic AMP/min/mg protein, $p < 0{\cdot}05$ for all, $n = 5$. Pretreatment of BAEC for 60 min with 100 nM staurosporine, an inhibitor of PKC, abolished the enhancement of adenylate cyclase activity caused by PMA ($p < 0{\cdot}05$) but had no effect on basal or stimulated adenylate cyclase activity in control or ATP pretreated cells. Neither PMA nor ATP pretreatment caused phosphorylation or the inhibitory guanine nucleotide-binding protein in BAEC ($n = 5$). There was no change in BAEC β adrenoceptor density after PMA pretreatment, measured by ^{125}I-iodocyanopindolol binding to BAEC membranes. Thus activation of PKC enhanced adenylate cyclase activity in BAEC. Extracellular ATP also enhanced adenylate cyclase activity, but independently of PKC.

Increased adenylate cyclase activity due to activation of PKC indicates the potential for crosstalk between second messenger systems in endothelial cells.

Increased fibrinolytic activity in the intima of atheromatous coronary arteries: protection at a price?

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Internal mammary artery, human saphenous vein, aorta, and coronary endarterectomy specimens from patients undergoing coronary surgery were crushed in polyethylene glycol solution and the supernatant assayed for tissue plasminogen activator (tPA) activity (using chromogenic substrate S2251) and protein content. Punch biopsies (2 mm) were taken and incubated on fibrin plates. Diameters of fibrinolysis were (mm (SE)): internal mammary artery (n = 8) 7·0 (0·9), saphenous vein (n = 10) 4·9 (0·7), and endarterectomy (n = 11) 10·4 (1·0). Endarterectomy specimens produced significantly larger areas of fibrinolysis compared with internal mammary artery (p = 0·03) and saphenous vein (p = 0·001) (Mann-Whitney U test). Extractable tPA activity was (mg tPA/mg protein (SE)): aorta (n = 7) 5·1 (0·9), internal mammary artery (n = 9) 5·4 (1·7), saphenous vein (n = 7) 4·1 (0·2), and coronary endarterectomy (n = 10) 27·6 (4·0). Coronary endarterectomy specimens had significantly more tPA activity than all other samples (p < 0·001) (Mann-Whitney U test). Antibody to tPA suppressed activity of endarterectomy supernatant. These data show that endarterectomy cores from coronary arteries exhibit greater fibrinolytic activity than normal veins or arteries.

Increased tPA activity in these vessels may help preserve patency but possibly at the expense of intimal instability and fibrous proliferation.

Effects of angiotensin converting enzyme inhibition on tissue renin and angiotensinogen gene expression

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Recent studies have shown the presence of renin and angiotensinogen mRNA in several tissues. To examine the effects of angiotensin converting enzyme inhibition on tissue renin and angiotensinogen gene expression male Wistar rats (n = 6, weight 300 to 400 gm) were treated for five days with 1·5 mg/kg/day perindopril administered by gavage. Control rats (n = 6) were given the vehicle (water). At the end of the treatment period plasma renin concentration was considerably higher in the perindopril group compared with the controls (317·0 (48·8) ng/ml/h *v* 9·4 (1·3) ng/ml/h) and the angiotensin II concentration significantly lower (<2·0 pg/ml *v* 11·0 (2·1) pg/ml). Renin and angiotensinogen mRNA concentrations were compared by northern blotting. For internal control, filters were also probed for mRNA and HGPRT. Perindopril treatment led to a greater than fourfold increase in kidney renin mRNA concentration. By contrast no significant differences were seen in renin mRNA concentrations in the brain, heart, adrenal, aorta, testes, and liver of perindopril treated and control rats. Likewise no significant change was found in angiotensinogen mRNA concentrations in any of the tissues of the treated group.

These results therefore indicate qualitative differences in feed back control of renin gene expression in renal and extrarenal tissues. Although tissue renin angiotensin systems may be important targets for the actions of angiotensin converting enzyme inhibitors, their short term administration does not cause significant changes in renin or angiotensinogen mRNA concentrations in several sites.

Detection of proliferating cells in human coronary artery

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Despite the lack of direct evidence, smooth muscle cell proliferation has been implicated in the development of atherosclerotic lesions in humans. To determine the location and degree of cell proliferation, immunohistochemistry with PC-10 antibody was performed on segments of human coronary artery obtained from our transplantation programme. This antibody is directed against the proliferating cell nuclear antigen (PCNA), which is known to accumulate in proliferating cells. Specific cell types were then identified on serial sections for smooth muscle cells (α actin), macrophages (Mac 387), and endothelial cells (Q-Bend 10). PC-10 positive cells were detected predominantly in the neointima and to a lesser extent in the medial layers. An intact endothelium was identified on top of the neointimal layers, which contained an abundance of macrophages and smooth muscle cells in a synthetic phase. Occasional macrophages were also seen in the media. By an established organ culture model the specificity of PC-10 for proliferating cells was then investigated. Segments of human coronary artery were maintained in culture for 14 days, pulse labelled with ^{3}H thymidine for the last 24 hours, and immunostained for PC-10 before autoradiography. By this double labelling technique it was shown that only a minority of PC-10 positive cells had incorporated ^{3}H thymidine.

Cell proliferation occurs in diseased human coronary arteries; PC-10, however, overestimates the number of actively dividing cells. This may simply reflect the long half life of PCNA or may be the result of growth factors from the vessel wall causing enhanced synthesis of the PCNA protein.

Electrophysiological assessment and follow up of survivors of cardiac arrest

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Few data are available on the long-term outcome of cardiac arrest survivors in the United Kingdom. Between July 1987 and June 1991, 37 patients were referred for assessment after resuscitation from a cardiac arrest not associated with acute myocardial infarction. The age range of the patients was 19 to 72 (mean 51·7) years. Diagnoses were coronary artery disease in 21 (with previous myocardial infarction in 17), dilated cardiomyopathy in six, valvular heart disease in three (one with concomitant coronary artery disease), Wolff-Parkinson-White syndrome in two, and miscellaneous in four. Twenty four patients had impaired left ventricular function and 16 had left ventricular ejection fractions of <30%. Twenty five received empirical antiarrhythmic drug treatment before referral and drug toxicity was implicated as a cause of cardiac arrest in three patients. Electrophysiological studies were performed in thirty five patients. Eighteen (group I) had inducible sustained monomorphic ventricular tachycardia, 15 (group II) had either no arrhythmias or non-specific arrhythmias inducible, and the two patients with Wolff-Parkinson-White syndrome had reciprocating tachycardia and rapidly conducted atrial fibrillation. Of the 18 patients in group I, six have been treated with drugs alone and 12 have had non-pharmacological treatment (implantable cardioverter-defibrillator in seven, surgery in two, percutaneous coronary angioplasty in one, transplant in one, antitachycardia pacemaker in one). Of the 15 patients in group II, three are on no treatment, two have had coronary artery bypass surgery, five have had defibrillators implanted, and five were prescribed antiarrhythmic drugs. At a mean follow up of 464 (405) days, 32 patients remain alive. The five who have died all had ejection fractions below 30% ($p = 0·01$), four were in group I, and one death was sudden.

With use of electrophysiological studies for risk assessment and treatment selection, many patients will require non-pharmacological treatment to prevent recurrence of cardiac arrest. The main determinant of survival appears to be left ventricular function, and with optimal treatment the risk of sudden death is low.

Efficacy and safety of dofetilide, a new class III antiarrhythmic agent, in recurrent ventricular tachycardia

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Concern about the safety and efficacy of class I antiarrhythmic drugs has prompted the development of potent new class III agents such as dofetilide, which selectively prolongs action potential duration and refractoriness by blockade of the delayed rectifier potassium current without depressing conduction or contractility. The short-term efficacy of dofetilide was evaluated at four dose levels in 39 patients with recurrent ventricular tachycardia (mean left ventricular ejection fraction 40 (13)%) inducible by programmed electrical stimulation (maximum three extrastimuli, 600 and 400 ms drive cycle lengths and two sites). Programmed stimulation was performed before and after intravenous administration of dofetilide as loading (15 min) and maintenance (45 min) infusions at doses of 1·5, 3·0, 6·0, and 9·0 mcg/kg. At 1·5 mcg/kg, there was no significant change in ventricular refractoriness or QTc and only 1/9 patients was non-inducible at restimulation. Doses of 3·0 to 9·0 mcg/kg all significantly prolonged ventricular effective refractory period (by 9·4 (15·5)%) and functional refractory period (by 7·8 (16·6)%) compared with baseline. Complete suppression of inducible ventricular tachycardia at all levels of stimulation was obtained in 11/30 of these patients, and ventricular tachycardia cycle length was slowed by > 100 ms in one case. The response rate at each of these three electrophysiologically active doses was similar. Acceleration of induced ventricular tachycardia compared with baseline was found in just one patient receiving 9·0 mcg/kg and there were no other adverse effects.

Intravenous dofetilide at doses of 3·0 to 9·0 mcg/kg prolonged ventricular refractoriness and achieved a response rate of 40% (12/30) with a low incidence of adverse effects. This favourable efficacy rate and excellent safety profile suggest that dofetilide should be further evaluated in the treatment of recurrent ventricular tachycardia.

Is QT interlead variability an arrhythmogenic marker?

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It has been suggested that increased QTc interlead variability (dispersion) on the surface electrocardiogram may be associated with high risk of serious ventricular arrhythmias. To determine whether QTc dispersion (calculated as maximum QTc—minimum QTc) can distinguish patients with from those without significant ventricular arrhythmias, we measured QTc interval in all leads of a surface electrocardiogram in 30 patients after myocardial infarction (aged 61 (7)) and 15 age matched normal control subjects. Fifteen myocardial infarction patients (group A) showed >30 single ventricular extrasystoles/h, or ventricular tachycardia, or both, and the other 15 showed <10 single ventricular extrasystoles/h and no ventricular tachycardia (group B). No myocardial infarction patients had evidence of conduction delays or were on antiarrhythmic medication. Myocardial infarction patients showed longer QTc (465 (21) *v* 418 (17) ms, $p < 0·01$) and greater QTc dispersion (75 (24) *v* 35 (9) ms, $p < 0·01$) compared with controls. Group A patients showed lower radionuclide ejection fraction (23 (4) *v* 36 (5)%, $p < 0·02$) and longer QTc (480 (17) *v* 440 (23) ms, $p < 0·05$) compared with group B; however, QTc dispersion was similar between groups A and B (79 (27) *v* 73 (20) ms respectively, NS).

Myocardial infarction patients show longer QTc and greater QTc dispersion compared with normal people; QTc dispersion alone, however, cannot distinguish myocardial infarction patients from those without serious ventricular arrhythmias.

Energy requirements of epicardial atrial defibrillation with bidirectional and monophasic waveforms

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Bidirectional waveforms are established in ventricular defibrillation, but their value in atrial defibrillation is unknown. We compared a monophasic and a bidirectional waveform in epicardial atrial defibrillation. The two waveforms were evaluated in 21 patients undergoing coronary artery bypass grafting. One hundred shocks were randomised, with up to six atrial shocks administered in each patient. The monophasic was an eight ms, truncated exponential waveform; the bidirectional was an eight ms, dual capacitor waveform with equal first and second phase duration and leading edge voltage. The first and second phases were separated by 0·01 ms. Delivered energy was controlled by the stored voltage. Cardiopulmonary bypass was achieved without cardioplegia by alternating cross clamping and ventricular fibrillation at a systemic temperature of 31°C. Atrial fibrillation was induced on bypass after the first venous graft by the application of A/C current to the right atrial appendage. Atrial shocks were delivered through customised, contoured, stainless steel paddles applied to the posterior left atrial wall (surface area 11 cm^2; cathode for the first phase) and to the anterior right atrial wall (surface area 26 cm^2; anode for the first phase). All shocks were synchronised with the ventricular R wave. For the monophasic waveform the delivered energy (Joules) associated with 50% success (E50) was 1 (0·8) and with 80% (E80) success was 3 (2·4); for the bidirectional waveform the E50 was 0·3 (0·1) ($p = 0·08$) and the E80 was 0·4 (0·1) ($p < 0·05$).

Less energy is required in epicardial atrial defibrillation with a bidirectional than a monophasic waveform. This may have implications for both transthoracic atrial defibrillation and possible future development of an implantable dual chamber defibrillator.

A new philosophical approach to the electrocardiographic diagnosis of ventricular tachycardia

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Ventricular tachycardia is the prognostically important differential diagnosis of a broad complex tachycardia, but the current electrocardiographic rules tend to result in the overdiagnosis of supraventricular tachycardia. This is due to the number and complexity of the rules for the diagnosis of ventricular tachycardia, and in their absence, the diagnosis of exclusion of supraventricular tachycardia. This study sought to reverse this strategy using simple rules, widely applicable in electrocardiographic diagnosis, for the positive diagnosis of supraventricular tachycardia, with ventricular tachycardia the diagnosis of exclusion. Supraventricular tachycardia was the diagnosis if the electrocardiographic pattern was typical of that produced by bundle branch block. Typical left bundle branch block pattern has an rS or QS wave in lead V1, and an R wave in lead V6. Typical right bundle branch block has an rSR′ pattern in lead V1 and an RS pattern in V6, the R greater than the S wave. Twelve lead electrocardiograms were collected from 102 patients with broad complex tachycardia (QRS width >110 ms), 69 with ventricular tachycardia and 33 with supraventricular tachycardia, the diagnosis established by electrophysiology. A single blinded observer reported on all the electrocardiograms. The correct diagnosis of ventricular tachycardia was made in 63/69 patients and the correct diagnosis of supraventricular tachycardia was made in 24/33 patients (sensitivity for ventricular tachycardia 91%, specificity 73%). All six patients with ventricular tachycardia who were misdiagnosed as supraventricular tachycardia had a left bundle branch block pattern and five had right ventricular outflow tachycardia, the diagnosis suggested on the electrocardiogram by right axis deviation in the frontal plane.

These criteria, for the differential diagnosis of broad complex tachycardia, only require knowledge of classical bundle branch block patterns and were highly sensitive for the more important diagnosis, ventricular tachycardia.

Adenosine-sensitive atrial tachyarrhythmias: clinical and electrophysiological characteristics

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Several groups have suggested the use of intravenous adenosine in the diagnosis of both narrow and broad complex tachycardias. The termination of an arrhythmia by adenosine is thought to be strongly indicative of a junctional, rather than atrial, origin of the tachycardia. We report the clinical and electrophysiological findings in 12 patients with sustained atrial tachyarrhythmias that were slowed or terminated by intravenous adenosine (mean dose 0·13 mg/kg). All patients underwent full diagnostic electrophysiological study. Mean age of the patients was 39·5 and three had evidence of structural heart disease. Seven patients had normal electrocardiograms during sinus rhythm, one had left bundle branch block, and four had evidence of ventricular pre-excitation. Six patients had evidence of sinus node re-entrant tachycardia at electrophysiological study: adenosine terminated tachycardia in 5/6 patients and slowed the tachycardia without termination in 1/6 patients. Three patients had atrial flutter with ventricular pre-excitation: in all three patients flutter rate was transiently accelerated before termination occurred. Three patients had an incessant atrial tachycardia that could not be terminated by atrial extrastimuli ("automatic" atrial tachycardia): adenosine slowed and then transiently terminated this arrhythmia in all three patients.

At least three forms of atrial arrhythmia may be terminated by adenosine. These findings have implications for both the mechanism of atrial arrhythmias and for the use of adenosine in the diagnosis of arrhythmias. Adenosine is likely to have a useful diagnostic role in distinguishing sinus node re-entrant tachycardia from physiological sinus tachycardia.

Waist: hip circumference ratio (WHR) and its relation to cardiovascular risk factors in men and women

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Because of the lack of prospective studies of risk factors for coronary heart disease in British women and the reported increase in the risk of coronary heart disease with high waist:hip ratio, we assessed the relation of waist:hip ratio to fasting plasma insulin and lipoprotein concentrations in a stratified random sample of 1048 women (aged 25 to 69) and 824 men (aged 40 to 69) who attended a health survey in East Bristol. Compared with women with low waist:hip ratio, women with high waist:hip ratio (>0·78) had higher concentrations of plasma insulin by 50% or 2·0 mU/l, total triglycerides by 45% or 0·47 mmol/l, total cholesterol by 10% or 0·5 mmol/l and total/high density lipoprotein cholesterol ratio by 13% or 1·0, but lower concentrations of total high density lipoprotein cholesterol by 11% or 0·16 mmol/l and high density lipoprotein subfraction 3 cholesterol by 13% or 0·12 mmol/l. Whereas men with high waist:hip ratio (>0·95) had higher concentrations of plasma insulin by 80% or 4·0 mU/l, total triglycerides by

21% or 0·32 mmol/l, total cholesterol by 16% or 0·72 mmol/l, and total high density lipoprotein cholesterol ratio by 14% or 0·7 but lower concentrations of total high density lipoprotein cholesterol by 8% or 0·09 mmol/l and high density lipoprotein subfraction 2 cholesterol by 8% or 0·03 mmol/l. All these were statistically significant, and independent of age, body mass index, smoking habits, alcohol consumption (and taking oral contraceptives) in women but not in men, using multiple regression analysis.

High waist:hip ratio is associated with high levels of several cardiovascular risk factors and waist:hip ratio is an independent predictor of coronary heart disease in women.

Relation of diet to current smoking and time since quitting in the Scottish Heart Health Study

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Recent publications have suggested that cigarette smoking is associated with other potentially detrimental lifestyles, and that the diet of current smokers differs from that of non-smokers. In the Scottish Heart Health Study data on smoking, including time since stopping smoking, have been related to analysis of a food frequency questionnaire in 4265 men and 4770 women. Male current smokers had a higher consumption of energy, sugar, and alcohol than never smokers. After adjustment for energy intake they had a lower consumption of polyunsaturated fat, fibre, and antioxidant vitamins. Ex-smokers were intermediate and, when analysed by time since stopping, showed a progression from the dietary pattern of smokers towards that of never smokers. In women similar differences occurred between smokers and never smokers but the ex-smokers more closely resembled the never smokers and did not exhibit the clear trends seen in men. In both sexes ex-smokers had smoked as much as the current smokers in the past. This cross sectional study suggests that current cigarette smoking is associated with an altered diet which takes some years to change back after stopping smoking. Coronary risk in smokers is therefore compounded by an impoverished diet.

Cardiorespiratory symptoms before loss of employment

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Unemployed men are far more likely to report a variety of health problems than employed men. There are two possible explanations for this: (*a*) Loss of employment leads to higher levels of ill health and (*b*) men who lose employment have higher morbidity before their loss of employment. In the British Regional Heart Study 7735 men aged 40 to 59 randomly selected from one general practice in each of 24 towns in England, Wales, and Scotland were examined between 1978 and 1980. The data analysed are from the 6057 men who were employed for the previous five years. At the examination, men who subsequently experienced unemployment or early retirement (before 65) were significantly ($p < 0.05$) more likely to report experiencing various cardiovascular and respiratory symptoms than men who remained continuously employed; 10·8% of continously employed men reported chest pain on exertion or an episode of severe chest pain and 22·4% reported experiencing chronic bronchitis, breathlessness, or wheeze compared with 13·7% and 30·6% respectively of men who subsequently became non-employed. Objective measurements followed the same pattern; 6·2% of continuously employed men had electrocardiographic evidence of ischaemic heart disease and 9·0% had measured poor lung function, compared to 7·0% and 11·6% respectively of men who subsequently became non-employed. Reporting any of the cardiorespiratory symptoms significantly increased the risk of experiencing some non-employment in the next five years. Experiencing breathlessness or chronic bronchitis carried the greatest risk of non-employment (RR = 1·43 and RR = 1·31 respectively.

In determining whether loss of employment leads to higher levels of ill health, the health of the men before loss of employment must be taken into account.

What do we do with survivors of out of hospital ventricular fibrillation?

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The deployment of more defibrillators and paramedics on ambulances is leading to increasing numbers of patients surviving out of hospital ventricular fibrillation. We reviewed the in hospital course and management of 42 such patients (31 men: 11 women, mean age 64, range 44 to 87) admitted to four hospitals. Sixteen patients (group 1) developed myocardial infarction, seven had possible myocardial infarction (group 2), and there was no evidence of myocardial infarction in 19 patients (group 3). Patients in group 3 were significantly more likely than those in group 1 to have a past history of ischaemic heart disease (12/19 *v* 5/16) and to be taking diuretics (10/19 *v* 3/16) (both $p < 0.05$), and less likely to have experienced chest pain before cardiac arrest (5/19 *v* 15/16) ($p < 0.001$). Thrombolytic treatment was administered to eight patients in group 1 and three patients in group 3, with appreciable bleeding complications in three cases. Within the first 24 hours five patients in group 1 and seven in group 3 had further cardiac arrest. Similar proportions of patients in each group received lignocaine, but more patients in group 3 required other anti-arrhythmic drugs during this time (11/19 *v* 3/16) ($p < 0.05$). At discharge more patients in group 3 were receiving anti-arrhythmics other than β blockers (12/19 *v* 2/16). Of those in group 3, only eight underwent 24 hour Holtor monitoring, four had exercise testing, five had echocardiographs, four underwent cardiac catheterisation, and two were referred for electrophysiological studies. Cardiologists were involved in the care of six of these patients, and saw five of the remainder in outpatient clinics.

The management of patients surviving prehospital ventricular fibrillation, particularly those at greatest risk of recurrent ventricular fibrillation, is inadequate, and is likely to remain so without increased cardiological input into their care and the development of management guidelines.

Streptokinase resistance is present two years after initial administration of streptokinase

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Thrombolytic treatment is an accepted therapy for acute myocardial infarction and streptokinase (SK) is the most commonly used agent in the United Kingdom; however, SK is antigenic and causes antibody formation that may affect the activity of a subsequently administered dose. To measure antibody mediated resistance to SK in the general population and after exposure to SK or streptococcal infection, venous blood samples were taken from 30 normal people, 40 patients admitted to a coronary care unit before and on days 4 and 10 after receiving SK, 12 patients one year after receiving SK, 12 patients two years after receiving SK, and 12 patients after proven streptococcal infection. Streptokinase resistance was measured by a dilution neutralisation assay (Neut, 625 u/ml being the concentration to neutralise 1·5 million units of SK), an enzyme linked immunosorbent assay (ELISA) to measure total IgG anti-SK antibodies and a fibrin plate lysis system (FPL, in vitro clot lysis in the presence of patients' serum, 100% lysis meaning no inhibition by the patients serum, 0% meaning complete inhibition). Anti-SK activity (mean (SD) for normal people was Neut 87 (10) u/ml, ELISA 28 (6·3) u/ml, and FPL 100 (4)% which were not different from day 0 values for the coronary care unit patients. In the coronary care unit patients anti-SK activity on day 0, day 4, and day 10 was 68 (6·1) u/ml, 375 (127)* u/ml, and 3667 (299)* u/ml for the Neut assay, 18 (4·5) u/ml, 38 (30·7) u/ml, and 311 (133)* u/ml for the ELISA, and 100 (9)%, 94 (8)% and 17 (14)%* for the FPL (*indicates p < 0·01 *v* day 0). Anti-SK activity was significantly raised (increased ELISA and reduced FPL values) in patients tested at one year (ELISA 120 (25) u/ml* and FPL 43 (9·7)%*), at two years (ELISA 198 (44) u/ml* and FPL 31 (19)%*), and after streptococcal infection (ELISA 177 (44)* u/ml and FPL 50 (10)%*) (*indicates p < 0·01 *v* normal controls). At both one and two years after SK administration 66% of patients had sufficient anti-SK activity to neutralise completely a standard dose of SK.

Thus whereas anti-SK activity is low in the population receiving SK for the first time, this activity develops early after treatment and is present in most patients for up to two years after the initial dose. Readministration of SK may be ineffective for at least two years.

Frusemide-induced natriuresis is augmented by ultra-low-dose captopril but not by standard doses of captopril in chronic heart failure

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We have studied whether a very low starting dose (1 mg) of the angiotensin converting enzyme inhibitor captopril might better preserve the natriuretic response to the loop diuretic frusemide in chronic heart failure than the conventional higher dose of 25 mg captopril, which tends to attenuate this response acutely. Ten patients with New York Heart Association grade II-III chronic heart failure and left ventricular ejection fractions of 24 to 42% were each treated on three occasions with oral frusemide plus placebo, 1 mg captopril, or 25 mg captopril in randomised double blind crossover fashion. As compared with placebo, 1 mg captopril caused only slight non-significant falls in mean arterial pressure and circulating angiotensin II (AII) concentration and had no effect on glomerular filtration rate, estimated as the elimination of ^{51}Cr-EDTA. By contrast, 25 mg captopril produced a considerable fall in mean arterial pressure (p < 0·0001), obvious suppression of serum AII concentration (p < 0·002), and a fall in glomerular filtration rate (p = 0·0007). Whereas 25 mg captopril caused moderate attenuation of frusemide induced natriuresis, 1 mg captopril augmented the natriuretic response to frusemide by 104% (p < 0·05 *v* placebo). In the face of frusemide induced renal arteriolar dilatation in chronic heart failure, captopril at a starting dose of 1 mg (but not 25 mg) preserves enough circulating AII to maintain efferent arteriolar tone and thus glomerular filtration, while augmenting the renal tubular natriuretic response to frusemide.

In a subgroup of chronic heart failure patients with intractable fluid retention, use of ultralow dose captopril, rather than conventional doses, may more effectively facilitate the natriuretic response to frusemide.

Response to candoxatrilat in patients with severe heart failure

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Candoxatrilat, a neutral endopeptidase inhibitor, has beneficial actions in patients with mild heart failure but there have been few studies in severe heart failure. Intravenous boluses of endoxatrilat (50 mg, 100 mg, and 200 mg) and placebo were given on separate days to 12 patients with severe heart failure (ejection fraction 36 (2)%) using a blinded four way crossover design. Blood pressure and urine output were measured two hourly for eight hours after each bolus. Renal blood flow and glomerular filtration rate were measured radioisotopically. Plasma hormones were measured before and three hours after dosing. There was no difference in response between the candoxatrilat doses tested. Compared with placebo, 100 mg candoxatrilat increased urine flow (56 (11) *v* 143 (24) ml/h, p < 0·01) and sodium output (3·6 (1·2) *v* 7·6 (1·5) mmol/h, p < 0·01). Diuresis was greatest up to four hours after the dose although effects persisted for at least six hours. Candoxatrilat increased urinary magnesium (p < 0·01) and cyclic guanosine monophosphate concentrations (p < 0·001) over eight hours but not potassium. Plasma aldosterone concentration fell (178 (41) *v* 103 (26) pg/ml, p < 0·01) but vasoactive intestinal polypeptide concentration increased (p < 0·05). Overall there were small increases in glomerular filtration rate and renal blood flow, and a fall in blood pressure (NS). In four patients, urine flow increased < 75% over the first four hours (mean 25%, range − 17 to 73%) with a fall in glomerular filtration rate (76 to 64 ml/min). In eight patients urine flow increased

>90% over the first four hours with an increase in glomerular filtration rate (70 (11) to 99 (9) ml/min, $p < 0.05$).

Unlike many reports with infusions of atrial natriuretic peptide, candoxatrilat causes diuresis in patients with severe heart failure.

Effect of sumatriptan (GR43175) on central haemodynamics and coronary circulation

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Sumatriptan, a selective $5HT_1$-like agonist is effective in the acute treatment of migraine. Its effects on coronary artery dimensions and central haemodynamics were assessed in 10 patients (six men, four women, age 52·9 (9·8)) undergoing diagnostic coronary angiography. Mean systemic arterial pressure, mean pulmonary artery pressure, heart rate, and 12 lead electrocardiogram were recorded at five min intervals during placebo infusion followed by a 10 min infusion of sumatriptan to a total of 48 μg/kg. Coronary artery dimensions were measured using digital calipers at identified segments on hard copy end diastolic frames obtained with digital subtraction angiography at baseline, and after each infusion. There were no changes in heart rate or electrocardiographic morphology with either infusion. Baseline measurements (mean (1 SD)) were mean systemic arterial pressure 100 (13·2) mm Hg, mean pulmonary artery pressure 15·2 (6·3) mm Hg, and mean coronary artery diameter 4·3 (1·6) mm. No significant change followed placebo infusion: mean systemic arterial pressure 99 (11·6) mm Hg, mean pulmonary artery pressure 16·2 (6·2) mm Hg, mean coronary artery diameter 4·2 (1·6) mm. Sumatriptan caused a vasoconstrictive response with increase in mean systemic arterial pressure to 115 (22·5) mm Hg ($p < 0.001$), mean pulmonary artery pressure to 25·5 (11·2) mm Hg ($p < 0.001$) and a reduction in coronary artery diameter to 3·6 (1·6) mm ($p < 0.001$) The mean percentage reduction from baseline in mean coronary artery diameter was 13·9 (9·6)% (confidence interval 10·9 to 16·9).

Sumatriptan, a selective $5HT_1$ agonist causes a vasopressor response in both pulmonary and systemic circulations with, in addition, coronary artery vasoconstriction.

Autonomic reflexes stimulated by coronary balloon angioplasty: regional differences in afferent population

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The sensory innervation of the heart is thought to be autonomically mediated although direct stimulation of the afferents has been poorly documented in humans. The aim of the study was to stimulate the afferents directly in patients undergoing elective percutaneous transluminal coronary balloon angioplasty (PTCA) and record efferent responses. Efferent responses measured by changes in heart rate, mean arterial pressure, plethysmographic forearm blood flow and resistance were compared in groups during balloon inflation of the left anterior descending artery (LAD), right coronary artery (RCA), and circumflex artery (CX). All balloon inflations were for at least 30 seconds and the maximal change recorded in that time. Ten male patients underwent PTCA to 10 lesions in the LAD artery, nine patients to 10 lesions in the RCA, and five patients to five lesions in the CX. The heart rate increased by 12·1 (5·2)% (mean (SEM)) in the LAD group and decreased by 6·1 (3·0)% in the RCA group ($p < 0.04$). It did not change in the CX group. Mean arterial pressure increased by 11·7 (2·9)% in the LAD group and decreased by 1·2 (1·9)% in the RCA group ($p < 0.002$). In the CX group, mean arterial pressure decreased by 0·9 (2·9)%, which was significantly different from the LAD group ($p < 0.02$). Forearm blood flow decreased by 34·3 (8·8)% in the LAD group and increased by 66·8 (33·0)% in the RCA group ($p < 0.01$). In the CX group, it increased by 49·3 (21·7)%, which was significantly different from the LAD group. Forearm resistance increased by 86·3 (13·5)% in the LAD group and decreased 11·3 (26·8)% in the RCA group ($p < 0.005$). In the CX group, it decreased by 22·7 (17·6)%, which was significantly different from the LAD group ($p < 0.0004$).

These data indicate that PTCA induces a reflex initiated by the heart. Angioplasty stimulation in the RCA and CX territory resulted in a vagally mediated reflex, and in the LAD territory, a sympathetically mediated reflex. This supports findings from animal studies that the inferior surface of the left ventricle has a predominantly vagal afferent innervation and the anterior surface a predomiantly sympathetic afferent innervation.

Comparison of angiography and intravascular ultrasound in the detection of early atherosclerosis

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The presence of arterial disease is recognised by angiography which relies on the visualisation of luminal narrowing but poorly differentiates the cause of narrowing, that is, thrombus, embolisation, spasm, or atheroma. In the absence of luminal narrowing an artery is usually assumed to be disease free. Our early experience with intravascular ultrasound suggested that we could detect changes in the intima and media of arteries in vessels that were angiographically normal. In vitro work has confirmed that atheroma can be clearly seen with intravascular ultrasound and that even the earliest changes of atherosclerosis produce a typical thickening of the intima. We have carried out in vivo studies of peripheral arteries in 15 patients to assess the sensitivity of intravascular ultrasound compared with angiography. We compared the findings of digital subtraction angiography with intravascular ultrasound in 29 segments of femoral and iliac artery. A haemostatic sheath was placed in the femoral artery. A 6 french intravascular ultrasound catheter (20 MHz) was inserted through the sheath and positioned at the iliac bifurcation. A radio-opaque ruler was placed at the level of the artery. A digital subtraction angiogram was taken using a hand injection of 10 ml of non-ionic contrast. The catheter was withdrawn at 2 mm intervals. Sequential images were recorded on video tape. The arteries were divided into 5 mm segments and the presence of stenosis or vessel wall irregularity noted from the angiogram and compared with the findings of the intravascular ultrasound images taken at the same positions within the artery. The images were regarded as abnormal if intimal thickening, plaque, or calcification were present. Of 29 segments studied 11 were angiographically abnormal. Twenty three segments were abnormal when studied by intravascular ultrasound including all the angiographically abnormal segments. Only 48% of abnormal segments as shown on intravascular ultrasound were thus detected by angiography.

Intravascular ultrasound is able to show atherosclerotic changes in angiographically normal arteries. Not only were very early intimal changes visualised by intravascular ultrasound but quite mature sizable plaques were frequently missed by angiography because of compensatory atrophy of the media underlying the plaque. Luminal encroachment occurs late in the development of atheromatous arterial disease, a fact that should be taken into account particularly in studies of atheroma regression.

Doppler derived transmitral velocity indices: changes occurring during alteration of ventricular preload

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It has been postulated that Doppler derived transmitral blood velocity indices reflect changes in left ventricular diastolic function. The relation, however, between left ventricular filling pressure, diastolic function, and transmitral Doppler indices remains uncertain. To examine this relation we studied 22 patients undergoing coronary artery bypass surgery and who had left ventricular ejection fractions >40%. Transmitral blood velocity was measured at varying filling pressures by transoesophageal echocardiography after opening of the pericardium and before initiation of cardiopulmonary bypass. Transmitral velocities were recorded in a basal state and after fluid loading. The maximum early diastolic filling velocity (Emax); the maximum velocity at atrial contraction (Amax); the E/A velocity ratio; the E wave maximum velocity/total diastolic time velocity integral (E/TVI); the mean acceleration slope (E accslope) and time (E acctime) to maximum E wave velocity; and the mean deceleration slope (E decslope) and time (E dectime) from peak E wave velocity linearly extrapolated to base line were recorded in both loading conditions. The total increase in pulmonary capillary wedge pressure was from 5·6 mm Hg (95% CI 4·5 to 6·7) to 10·0 mm Hg (8·7 to 11·4) ($p < 0{\cdot}0005$). Emax increased from 39·5 cm/s to 59·5 cm/s ($p < 0{\cdot}0001$); Amax increased from 56·1 cm/s to 67·9 cm/s ($p < 0{\cdot}0001$); the E/A ratio increased from 0·73 to 0·91 ($p < 0{\cdot}0001$); E accslope increased from 502 cm/s^2 to 640 cm/s^2 ($p < 0{\cdot}001$); E acctime increased from 89·9 ms to 100·5 ms ($p < 0{\cdot}025$); and E desclope increased from −186 cm/s^2 to −279 cm/s^2 ($p < 0{\cdot}003$); E dectime and E/TVI showed no significant change.

Changes in left ventricular filling pressure can significantly alter Doppler derived transmitral velocity indices and therefore this needs to be taken into account when trying to relate transmitral blood flow and diastolic function.

Ventricular tachyarrhythmias after myocardial infarction: what does surgery offer?

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Abolition of arrhythmia is the ultimate goal of treatment in patients with recurrent ventricular tachyarrhythmias after myocardial infarction. Whereas map guided endocardial resection can achieve this, it remains underused because many view the overall risk of surgery for these patients as unacceptably high. The aim of this analysis was to define the risk of endocardial resection for clinically recognisable patient subgroups by relating outcome to the clinical context in which surgery was performed. In the period 1980–91 endocardial resection was offered to all patients referred to this unit with life threatening drug refractory ventricular tachyarrhythmias regardless of age, time from acute myocardial infarction, or ventricular function. One hundred patients underwent endocardial resection, which was conducted in a uniform way throughout the study period. Mean age of patients was 56 (10) years, 81 were men and the myocardial infarction was anterior in 71. Mean left ventricular ejection fraction was 28% (range 5 to 50%) and 60 had a left ventricular aneurysm. The mean number of major ventricular tachyarrhythmic episodes per patient was 11 (range 2 to 200) and drug failures 4 (2). Emergency surgery was required for intractable ventricular tachyarrhythmias in 28 patients, and 32 of the total had surgery within eight weeks ("early") of acute myocardial infarction. Endocardial resection was performed in all. In addition aneurysmectomy was performed in 57, cryoablation of lesions in 26, and antiarrhythmic ventriculotomies in 11. Twenty five patients died within 30 days of surgery, 21 in low output cardiac failure. There have been no postoperative deaths from arrhythmias and only six patients required antiarrhythmic drug treatment. Outcome within 30 days of endocardial resection was critically related to the clinical context in which surgery was undertaken. Thus mortality for elective endocardial resection more than eight weeks after myocardial infarction, "early" post-myocardial infarction, emergency endocardial resection, and "early" emergency were 18%, 34%, 46%, and 56% respectively. The high overall mortality reflects the type of patients undergoing endocardial resection at this unit. Actuarial survival rates for the total group at one, three, and five years after surgery were 70%, 68%, and 66% respectively.

Surgery offers a cure of ventricular tachyarrhythmias at a risk proportional to the patient's preoperative risk of sudden death. It has a unique role in patients with intractable ventricular tachyarrhymia and has yet to achieve its full potential.

Discrimination of ventricular tachycardia from exercise induced sinus tachycardia by pulsatile right ventricular pressure monitoring

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The increasing complexity of implantable cardioverter defibrillators (ICDs) with the introduction of tiered treatment devices has expanded their application to include patients with slower pace terminable arrhythmias; however, rate criteria alone are not always sufficient to differentiate physiological tachycardia from haemodynamically stable ventricular tachycardia (VT). We have studied the use of right ventricular pulse pressure (RVPP) monitoring in distinguishing exercise induced sinus tachycardia from VT. The RVPP was recorded from 11 patients with recurrent VT (age 35–70; left ventricular ejection fraction 20–65%, coronary heart disease 8/11) during treadmill exercise testing and induced VT. Pressure signals were obtained via a percutaneous micromanometer catheter (Telectronics Pacing Systems), digitised at 1 kHz with a bandwidth of dc-250 Hz, and stored on optical disc before analysis. The RVPP and maximum dP/dt (dP/dt max) during peak exercise and sustained haemodynamically stable VT were expressed as a percentage of resting sinus rhythm values. Peak heart rate during exercise ranged from 78 to 187 beats/min. Heart rate during VT ranged from 139 to 225 bpm. Mean RVPP fell to a greater extent than dP/dt max during induced VT (to 63 (33)% *v* 83 (49)%) but both increased greatly during exercise (176 (46)% *v* 234 (79%). With a 30% fall compared with baseline sinus rhythm as a cut-off, RVPP diagnosed VT correctly in 9/11 patients (sensitivity 82%, specificity 100%) whereas dP/dt max only diagnosed VT correctly in 4/11 patients (sensitivity 36%, specificity 100%).

Preliminary results suggest that VT may be discriminated from physiological tachycardia with a high degree of specificity using measurement of RVPP and dP/dt max, but that the greater sensitivity of RVPP may be more suitable for clinical application. In the future, ICDs incorporating RVPP monitoring may allow increased use of antitachycardia pacing where previously distinction between VT and sinus tachycardia was not possible.

Fractionation of paced ventricular electrograms in hypertrophic cardiomyopathy is associated with an increased risk of sudden death

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Myofibrillar disarray in hypertrophic cardiomyopathy may cause dispersion of activation throughout the myocardium and this dispersion may form the substrate of ventricular fibrillation. Variations in myocyte dimensions may cause differences in conduction velocities and refractory periods and myocyte disarray may provide a number of conduction paths between two sites that may be recruited or blocked according to the refractory state of the intervening tissue. This hypothesis was tested in 37 patients with hypertrophic cardiomyopathy, of whom four had out of hospital ventricular fibrillation, five had ventricular tachycardia on ambulatory monitoring, 15 had a family history of sudden death, and four controls were studied by pacing one site in the right ventricle and recording electrograms from three other right ventricular sites. Intraventricular conduction curves were obtained with S1S2 coupling intervals decreasing in 1 ms steps from 479 ms to ventricular effective refractory period. These curves were repeated by pacing each right ventricular site in turn. The electrograms were high pass filtered to emphasise fractionation and two parameters: the point at which latency increased by 0·75 ms over a change of 20 ms in the S1S2 coupling interval and the increase in electrogram width between a coupling interval of 350 ms and ventricular effective refractory period were extracted. Linear discriminant analysis showed that patients with ventricular fibrillation, ventricular tachycardia, or family history of sudden death had increased electrogram width and early increase in latency and form a group that was distinct from low risk patients and controls ($p < 0·0000001$). Patients with ventricular fibrillation had the most pronounced electrogram widening and early increase in latency, and fell into a distinct group compared with the remaining patients ($p < 0·0001$).

This novel technique shows a consistent electrophysiological abnormality in hypertrophic cardiomyopathy and warrants prospective testing as a predictor of the risk of sudden death.

Inhibition in the human heart by long duration subthreshold pulses: spatial and temporal effects

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Termination of tachycardias by non-propagated stimuli has been reported, but the mechanism of this effect is not clear. We have shown that long duration subthreshold cathodal constant current pulses can produce large degrees of inhibition in the human heart, and this might be a possible mechanism for termination of tachycardia. We investigated further the effect of inhibition in 12 patients undergoing electrophysiological studies. Constant ventricular pacing (S1S1 = 600 ms) was performed, and effective refractory period was determined with a premature beat (S2) with an amplitude of twice the late diastolic threshold. The S1S2 interval was set at effective refractory period + 10 ms, and a cathodal conditioning pulse (Sc, duration = S1S2) was introduced, beginning synchronous with S1, and increased in amplitude until S2 failed to capture. The duration of Sc was then reduced in steps of 5 to 10 ms, leaving a gap between Sc and S2. Inhibition was shown to occur across gaps of up to 50 ms (mean 39 ms) with Sc amplitudes below late diastolic threshold in twelve patients; with further increases in Sc amplitude, inhibition could be produced more than 100 ms beyond the end of Sc. In a further eight patients we investigated whether an inhibitory effect could be produced at an adjacent pole on the same catheter; S1 and S2 were delivered as already described, and Sc (duration 10 to 20% longer than S1S2) was introduced at another point 1 to 5 mm away. Subthreshold values of Sc did not inhibit capture by S2; even when Sc amplitude was increased up to five times late diastolic threshold, no inhibition could be produced at a point 1 mm away.

These studies suggest that termination of tachycardia by subthreshold pulses is only feasible with a catheter positioned very close to a critical point on a re-entrant circuit. Termination of tachycardia by a non-propagated impulse is more likely to occur by local capture.

Relation between QT intervals and epicardial monophasic action potential

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To test the hypothesis that QT dispersion (QT max minus QT min) measures risk of arrhythmia by reflecting dispersion of ventricular recovery at the body surface monophasic action potential, studies were performed in eight patients undergoing routine cardiac surgery.

Monophasic action potentials were recorded from 10 left and two right ventricular sites with a reference electrode used to measure activation. Recordings were made in sinus rhythm and then with left ventricular pacing (to increase dispersion of ventricular recovery). Simultaneous 12 lead electrocardiograms were recorded at 50 mm/s. Mean dispersion of ventricular recovery time (activation time plus repolarisation time) in sinus rhythm was 53 (12) ms and increased to 86 (26) ms ($p = 0{\cdot}01$) with pacing. Mean QT dispersion in sinus rhythm was 43 (10) ms and also increased on pacing to 92 (27) ms ($p = 0{\cdot}001$). There was a positive correlation between the change in dispersion of ventricular recovery time produced by pacing and the change in QT dispersion (Spearman's $\rho = 0{\cdot}76$, $p = 0{\cdot}02$). Dispersion of ventricular recovery by pacing was almost entirely due to increased dispersion of activation time (mean increase = 46 (26) ms, $p = 0{\cdot}001$).

This study correlates body surface electrocardiographic QT measurements with perioperative monophasic action potentials in humans and shows a close relation between the two. Changes in QT dispersion induced by ventricular pacing correlate well with changes in the dispersion of ventricular recovery. As hypothesised QT dispersion does reflect dispersion of ventricular recovery.

Dobutamine is the most physiological stress for echocardiographic assessment of regional wall motion in multivessel coronary artery disease

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Stress echocardiography is being evaluated for the detection of reversible wall motion abnormalities in ischaemic heart disease before and after revascularisation. To assess the degree to which a variety of stresses reproduce the wall motion abnormalities of physiological exercise we studied a group of patients with resting left bundle branch block and angiographically proven multivessel coronary artery disease in whom the target lesion could not be determined by conventional angiographic or exercise electrocardiographic criteria. All patients underwent echocardiography during maximal treadmill exercise, incremental atrial pacing, infusion with adenosine (0·15 mg/Kg), high dose dipyridamole (0·84 mg/Kg), and incremental doses of dobutamine to maximal predicted heart rate or ischaemic endpoints. All pharmacological agents were well tolerated. Two subjects developed non-sustained ventricular tachycardia with dobutamine but both had histories of angina related ventricular tachycardia. There was no evidence of rate or ischaemia related changes in conduction. Overall regional wall motion indices were assessed on an established numerical grading of 1 to 4(1-normal, 2-hypokinetic, 3-akinetic, 4-dyskinetic) using a 21 segment system. Echocardiograms were analysed by two independent observers without knowledge of the stress mode or angiographic findings. Overall regional wall motion indices at rest were 1·87 (0·77) and increased significantly during exercise (2·22 (0·7)) and dobutamine infusion (2·28 (0·75)) ($p < 0{\cdot}05$) but did not alter significantly with atrial pacing (1·89 (0·81)) or dipyridamole infusion (1·73 (0·65)) and actually fell during adenosine infusion (1·73 (0·6)) (NS). Stress induced regional wall motion abnormalities all corresponded to a region of myocardium subtended by a stenosed epicardial coronary artery and no individual segment score altered in a direction against the trend for a particular stress.

Only dobutamine produces equivalent physiological stress to treadmill exercise in patients with multivessel coronary artery disease as judged by overall regional wall motion indices and individual segment behaviour.

Prognostic value of dobutamine echocardiography in patients with high pretest likelihood of coronary artery disease

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To investigate the usefulness of inducible regional asynergy on dobutamine stress echocardiography (DE) as a non-invasive predictor of future cardiac events. Fifty one symptomatic patients (age 54 (9), 45 men) with suspected coronary artery disease were studied using incremental doses up to 20 μg/kg/min. Pretest likelihood of coronary artery disease was 79·7 (SE 5·6)% before, and 83·4 (5·2)% after exercise electrocardiography with probability analysis based on age, sex, and symptoms. Cross sectional images were analysed by scoring an 11 segment model (normo or hyperkinesis = 1, hypokinesis = 2, akinesis = 3, dyskinesis = 4) and gave good interobserver agreement ($\kappa = 0{\cdot}77$). During 24 (4) months (range 19 to 32) of follow up 23 patients had cardiac events (one myocardial infarction, nine unstable angina, 10 coronary bypass surgery, three coronary angioplasty) and 28 were event free. Age, proportion with baseline asynergy (8/23 *v* 6/28), and echocardiographic ejection fraction (modified Simpson's rule; measurable in 33) were similar in these 2 groups (all NS). A positive DE was seen in 17/23 (74%) with and 8/28 (29%) without events ($p = 0{\cdot}003$, 95% CI 14 to 69); 5/6 (83%) patients with involvement of three segments had events. Myocardial infarction or unstable angina occurred in 8/25 (32%) with a positive, and 2/26 (8%) with a negative DE ($p = 0{\cdot}07$). Concordance between exercise electrocardiography and DE was 73%, and both exercise duration (389 (195) *v* 517 (237) s, $p < 0{\cdot}05$) and time to diagnostic ST shift (291 (192) *v* 447 (212) s, $p = 0{\cdot}05$) were shorter in those with inducible asynergy.

These data suggest that patients with probable coronary artery disease who have a positive DE are at higher risk of an adverse outcome. Thus DE may aid selection for coronary angiography and prognostic revascularisation, particularly in patients unable to exercise.

Inotropic versus vasodilator agents for diagnostic stress echocardiography: a prospective study in 100 patients undergoing coronary arteriography

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Both inotropic and vasodilator agents have been combined with echocardiography for the diagnosis of coronary disease. The purpose of this study was to establish the optimal stress by comparing dobutamine echo (DE) and adenosine echo (AE), in the same patients and conditions. One hundred patients without evidence of previous infarction, undergoing coronary arteriography for clinical indications, were studied prospectively by DE and AE at the time of arteriography. Dobutamine was infused during clinical, electrocardiographic, and echocardiographic monitoring, in three-minute increments from five to 40 mcg/kg/min. Adenosine was infused under the same conditions, initially at 0·10 mg/kg/min, with three-minute stages at 0·14 and 0·18 mg/kg/min. In each case, the stress protocol was terminated at completion (peak dose, >85% age predicted maximum heart rate, or appearance of severe ischemia), or the development of intolerable side effects. Digitised echo images before, during, and after stress were stored in a quad-screen, cine-loop display, and were evaluated qualitatively by independent observers. The DE protocol was completed in 68 patients and that for AE in 70 patients (NS). The commonest limitation for DE was hypotension (n = 15), whereas that for AE was dyspnoea (n = 14). All side effects were reversible and no serious complications occurred. The peak heart rate achieved at DE exceeded that at AE (111 (24) *v* 92 (15), p < 0·001) as did the increment in heart rate during the test (20 (5) *v* 14 (3) p < 0·001), and the peak rate pressure product achieved (42·7 (20·1) *v* 21·6 (10·9) $\times 10^3$, p < 0·001). In 62 patients with significant coronary disease (defined by the quantitation of >50% stenosis in a major epicardial vessel), the sensitivity of DE was 84%, and that of AE was 56% (p < 0·001). This difference was more prominent in the 32 patients with single vessel disease (81% *v* 50%, p < 0·01) than in those with multivessel disease (87% *v* 63%, p = 0·07). The specificity of DE was 82%, and that of AE was 92% (NS).

Thus DE has a significantly higher sensitivity than AE for the detection of coronary disease, and is the test of choice for pharmacological stress echo.

A comparison of exercise echocardiography and technetium-99m MIBI SPECT in three dimensional images for identification of myocardial ischaemia

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Exercise echocardiography is useful in the detection of myocardial ischaemia but has not been compared to technetium-99m metoxyisobutylisonitrile single photon computed tomography in three-dimensional images (SPECT). Fifty eight patients (37 men, 21 women; mean age 55·9 (9·4)) with recurrent episodes of angina of effort were studied. Abnormalities of left ventricular wall motion and thickness on exercise echocardiography and perfusion defects on SPECT suggesting myocardial ischaemia were compared with coronary angiography. The results obtained with both of these techniques were then compared with each other. The findings on exercise echocardiography correlated with those on coronary angiography in 52 (89·7%) of the 58 patients (p < 0·0001, κ = 0·817). Exercise echocardiography detected 42 (87·5%) of 48 patients with significant (>75% stenosis) coronary artery disease in at least one vessel on coronary angiography. All of 10 patients with normal coronary angiograms had normal findings on exercise echocardiography (specificity 100%). The findings of exercise SPECT correlated with those on coronary angiography in 35 (60·3%) of 58 patients (p < 0·0001, κ = 0·344). Exercise SPECT detected 34 (70%) of 48 patients with significant coronary artery disease. Ten out of 10 with normal coronary angiograms had normal exercise SPECT results (specificity 100%). The concordance of exercise echocardiography with exercise SPECT in identifying myocardial ischaemia was 63·8% (p < 0·0001, κ = 0·384).

Exercise echocardiography is a highly sensitive and specific non-invasive technique useful in the evaluation of patients with ischaemic heart disease. Its greater sensitivity may render it a more useful investigation than SPECT in the detection of underlying coronary stenoses.

Simultaneous dipyridamole stress echocardiography and technetium-99m MIBI SPECT after uncomplicated infarction: comparison of prognostic values with exercise testing

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To compare the frequency of "ischaemia" seen during simultaneous dipyridamole echocardiography and technetium 99m metoxyisobutylnitrile single photon emission computed tomography (SPECT), and compare their prognostic values with exercise electrocardiography, 90 patients with uncomplicated myocardial infarction underwent pre-discharge dipyridamole testing and those fit had maximal bicycle ergometry. Dipyridamole (0·84 mg/kg) was infused intravenously with continuous echo recording. Two minutes after dipyridamole, 370 MBq Tc-99m MIBI was injected intravenously. Stress SPECT images were acquired one hour later and rest images acquired 24 hours after stress. SPECT reversible perfusion defects occurred in 49/90 (54%) patients and echocardiographic new wall motion abnormalities in 31/88 (35%) patients with assessable echoes (p < 0·02). Of 66 patients fit for exercise testing, 33 (50%) had ST depression and 28 had a negative test (no ST depression with achievement of ⩾100 W workload). Eighty six patients were reviewed at a mean of 47 weeks after myocardial infarction; death had occurred in five of 30 with positive and one of 54 with negative dipyridamole echo (p = 0·02), in four of 47 with positive and two of 39 with negative SPECT (p = 0·43) and in none of the 25 patients with negative exercise tests.

After uncomplicated myocardial infarction, dipyridamole echocardiography or SPECT is a feasible alternative to exercise testing and dipyridamol echocardiography is a better predictor of subsequent cardiovascular death than SPECT.

Abnormalities of left ventricular wall motion in ischaemic heart disease: a comparison of Doppler echocardiography and magnetic resonance velocity mapping

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Abnormal ventricular relaxation is an early marker of ischaemic heart disease. Diastolic flow through the mitral valve is a global measure of ventricular filling affected by ventricular relaxation and this is commonly assessed by Doppler ultrasonography. Regional abnormalities may be even more sensitive and we have compared regional measurements of myocardial velocity measured by magnetic resonance velocity mapping with mitral flow measured by Doppler ultrasonography. Eighteen patients (mean age 62, range 42–78, 16 men) with coronary artery disease were studied after discontinuing cardiac medication. Twelve had suffered previous myocardial infarction. Doppler indices measured were peak mitral flow velocity during early diastole (E vel) and atriosystolic contraction (A vel), isovolumic relaxation time (IVRT), and time to E vel. The velocity ratio (E/A ratio) and peak rapid acceleration were derived. Cine magnetic resonance mapping of myocardial velocity perpendicular to a basal short axis plane was performed on the same day as the Doppler study and at similar heart rates. Velocity time curves were constructed in each of 16 sectors with measurement of the peak and mean early diastolic velocity and the number of segments with less than 50% of peak velocity (N). These parameters thus measured the severity and extent of abnormality respectively. There was a strong inverse correlation between N and E vel ($r = -0{\cdot}72$, $p < 0{\cdot}001$) and between N and E/A ($r = -0{\cdot}68$, $p < 0{\cdot}01$), and a strong positive correlation between mean peak myocardial velocity and E vel ($r = 0{\cdot}8$, $p < 0{\cdot}001$); A vel and IVRT did not correlate well.

Thus we have defined a new measure of regional diastolic ventricular function and have shown that regional abnormalities of wall motion during early diastole have a significant effect on left ventricular filling.

Objective evaluation of skeletal muscle counterpulsation in a mock circulation model

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It is important to assess the haemodynamic benefit of extra-aortic skeletal muscle counterpulsation before its clinical use. This has been investigated in 12 animals (sheep) using a mock circulation model. The model consists of a closed system of two Windkessel compliance chambers joined together by a latex tube, around which the muscle can be wrapped in a manner similar to that in vivo. In each animal, the left latissimus dorsi muscle was electrically stimulated at a standard stimulation regimen: pulse amplitude three volts, burst frequency 35 Hz, burst duration 240 ms, pulse width 240 μs, in the 1:4 mode. The time course of stimulation extended to five months: two weeks (two animals); one month (three animals); three months (two animals); four months (two animals); five months (two animals). The length of the wrap was eight cm in all animals. The results show that counterpulsation at 1:4 and 1:2 modes is more effective than in the 1:1 mode. After one month of conditioning, the mean volume displacement (cm^3) was 18·4 (0·4) in the 1:4 mode, 17·9 (0·4) in the 1:2 mode, and 15·0 (0·5) in the 1:1 mode, and the average peak pressure augmentation (mm Hg) was 17·5 (0·9), 17·1 (0·5), and 14·4 (0·5) respectively. A similar trend was found at the other time courses. Stimulation resulted in muscle fibre type transformation; at one month there was conversion to a 75% mixed fibre type population expressing fast and slow isoforms. Fibre type transformation was accompanied by loss of power from 14·8 Watts/kg (unconditioned muscle) to 8·9 Watts/kg (after five months of conditioning). The development of fatigue resistance was confirmed by the fact that in all animals the conditioned muscle completed a vigorous 30 minute fatigue test ending with a stimulation regimen of 5 V, 85 Hz in the 1:1 mode.

The results suggest that extra-aortic skeletal muscle counterpulsation does have the capacity to provide effective haemodynamic benefit and this may have a role in the treatment of patients with end stage cardiac failure.

Long-term follow up of patients requring intensive in-hospital support who underwent urgent cardiac transplantation

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There is concern about referring severely ill patients, who require active in hospital support, for cardiac transplantation, especially with the shortage of donor organs. Twenty six of 33 patients requiring such support with intravenous infusions of cardiac drugs and diuretics (32), in addition to balloon counterpulsation (16), peritoneal dialysis (7), pacing (3), and ventilation (2) as required, underwent urgent cardiac transplantation between January 85 and December 86. Twenty (78%) patients survived to hospital discharge, five more died at 10 weeks and 33, 36, 48 and 72 months. Fifteen patients remain alive and well at a mean of 63·5 months (range 56 to 78 months) after urgent cardiac transplantation (57·7% of those undergoing cardiac transplantation). Ten are working full time. They had a mean pretransplant ejection fraction of 11%, and a mean of 2·7 infusions (range 1 to 5) of inotropic/vasodilator drugs. Three required balloon counterpulsation and four emergency resuscitation at some point during admission before transplantation. Sixty six per cent had derangement in liver function, with >50% having renal dysfunction.

The long term results of severely ill patients undergoing urgent cardiac transplantation are very good, both in terms of survival and quality of life. Patients not requiring renal dialysis or balloon counterpulsation before transplantation seem to do particularly well. There seems little reason to exclude those who require inotropic and other supports or those who have evidence of non-critical hepatic or renal dysfunction from cardiac transplantation.

Predictive value of pulmonary haemodynamic measurements in patients accepted for cardiac transplantation

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This study investigated the predictive value of pulmonary haemodynamic measurements on survival after, or while awaiting, cardiac transplantation. In patients with raised resistances, the acute response to pharmacological manipulation was assessed to determine whether successful lowering of resistances conferred an improved survival potential. Right heart catheterisation was performed in 78 patients accepted on to our transplant programme. Transplant survivors (S, n = 58) were compared with patients dying within 30 days of operation (TxD, n = 8) and on the waiting list (WLD, n = 12). Levels of pulmonary hypertension (right ventricular systolic: S49 (14), TxD 54 (12), WLD 58 (16) mm Hg, mean pulmonary artery: S34 (10), TxD 35 (9), WLD 40 (12) mm Hg) were not significantly different, nor predictive of outcome. Transpulmonary gradient (TPG) was higher in patients who died (S9 (4), TxD 11 (3), WLD 13 (7) mm Hg, p = 0·015) and TPG ⩾ 12 was predictive of mortality, p = 0·016, with sensitivity (sens) 58%, specificity (spec) 76%, predictive accuracy (pa 71%). Pulmonary arteriolar resistances (PAR) were lower in survivors (S 2·4 (1·3), TxD 3·2 (2·9), WLD 3·6 (2·3) Units (U), p = 0·008) and PAR ⩾4 was predictive of mortality, p = 0·006; sens 42%, spec 91%, pa 78%. Indices of PAR were lower in survivors (S 4·2 (2·1), TxD 5·4 (3·2), WLD 6·5 (3·9) U × sq.m, p = 0·005) and PAR index > 8 predicted mortality, p = 0·014; sens 32%, spec 93%, pa 77%. All groups had similar cardiac indices, mean right atrial, and pulmonary artery wedge pressure measurements. Thirteen patients had raised PAR > 4 U. Seven underwent acute pharmacological manipulation, and PAR fell below 4 U in four patients, two of whom died. In total, eight patients with PAR > 4 were transplanted and three died (38%).

This study shows the importance of pulmonary haemodynamic indices in the assessment of potential cardiac transplant recipients. Patients with TPG ⩾ 12 mm Hg, PAR ⩾ 4 U, or PAR index ⩾ 8 U × sq m had reduced survival potential irrespective of whether transplantation was performed. In patients with raised PAR, the initial value is of greater predictive value than the response to pharmacological manipulation.

Surgical management of end stage heart disease: is conventional surgery still an option?

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In a selected group of patients referred for cardiac transplantation, conventional cardiac surgery may still represent an important alternative method of treatment. We audited our experience of this approach between January 1979 and June 1991. Of the 1398 referrals for cardiac transplantation, 52 patients (3·7%) were considered suitable for conventional cardiac surgical intervention, while 433 underwent cardiac transplantation. Of the 52 patients treated with conventional cardiac surgery, 40 (76·9%) underwent coronary artery bypass grafting, including 15 left ventricular aneurysmectomies, 10 (19·2%) cardiac valve replacements, and two (3·8%) had valve replacement and coronary artery bypass graft procedures. In hospital mortality (< 30 days) occurred in seven (13·5%) patients in the valve replacement group and two (3·8%) in the coronary artery bypass group. The overall actuarial survival for the patients undergoing heart transplantation at one, three, and five years respectively was 75% (2·1), 69% (2·4) and 62% (2·8). The overall actuarial survival for the patients undergoing conventional surgery at one, three, and five years was 80·2% (5·6), 69·2% (6·7), and 55·8% (7·6). Of the 45 hospital survivors after conventional surgery, 12 patients (26·7%) eventually received transplantation at a mean of 28·8 months (25·4). The one, three, and five year actuarial survival for the 40 patients who had coronary artery bypass surgery is 89·6% (4·9), 80·8% (6·6), and 63·0% (8·7). Three patients of the 10 (33·3%) in the valve replacement group died within 30 days of surgery and four died between five and 19 months after surgery and one patient underwent transplantation at 24 months; the remaining two are well at 119 and 61 months. New York Heart Association (NYHA) classification improved in most hospital survivors after conventional surgery (NYHA class preoperatively, III = 20 patients (38%), IV = 32 (62%) and postoperatively, I = 12 patients (43%), II = 14 (50%), III = two patients (1%)).

In a selected group of patients referred for transplantation, conventional surgery may represent a suitable option offering improved survival and functional state.

Accelerated coronary sclerosis in children after cardiac transplantation: what role do oral steroids have?

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Since August 1984, 98 children under the age of 15 years have undergone cardiac transplantation at Harefield Hospital. Their ages were between seven days and 14·8 years (mean 6·4 years). The indications were cardiomyopathy in 71, congenital heart disease in 25 and Kawasaki's disease in two. After transplantation, patients were maintained on cyclosporin A and azathioprine only. Routine steriods were not given. Acute rejection in this group was detected by non-invasive methods and routine biopsies were not performed. Sixty one patients have been followed up for more than one year (1·2 to 7·4 years) and 58 (95%) have undergone routine cardiac catheterisation and selective coronary angiography, irrespective of age, on 137 occasions. Right heart pressures and left ventricular end diastolic pressure was normal in all patients. In an attempt to diagnose accelerated coronary sclerosis, the coronary angiograms were reviewed by at least two independent observers. Only 1/137 angiogram was judged to be abnormal. This occurred six years after transplantation. One child, who did not undergo his routine angiogram at 12 months, died at 18 months from coronary occlusion and another child who died of chicken pox, six months after a "normal" angiogram was found to have coronary sclerosis at post mortem. Both these children were receiving steroids for conditions unrelated to their transplant. None of the other four late deaths were found to have coronary sclerosis at post mortem. Risk factors for coronary sclerosis were reviewed. There was no correlation with the number of rejection episodes but 2/4 children receiving routine steroids, as opposed to 1/57 not on steroids, developed this life threatening complication.

In the absence of routine steroids, accelerated coronary sclerosis is rare in children after cardiac transplantation.

Creatine kinase (CK-MB) isoforms as a non-invasive marker of significant acute allograft rejection after heart transplantation

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Frequent routine surveillance by right ventricular endomyocardial biopsies is necessary in cardiac transplant patients in their first postoperative year, to detect significant acute cardiac allograft rejection. Biopsy procedures carry an associated morbidity, a tendency to sample old biopsy sites, and inconvenience to the patient. Detection of the creatine kinase (CK)-MB2 isoform in plasma, as a sensitive marker of myocardial cell injury, is now possible. Measurement of the MB2/MB1 ratio has been used in the early diagnosis of acute myocardial infarction, when the total CK-MB isoenzyme activity is within the normal range. This study assessed CK-MB isoform measurement as an early non-invasive marker of allograft rejection after cardiac transplantation. Plasma samples were collected from 16 orthotopic heart transplant recipients before endomyocardial biopsy. The CK-MB isoforms were determined by high resolution agarose gel electrophoresis and quantified by densitometric scanning. 9/16 patients had 10 episodes of allograft rejection; the total CK-MB isoenzyme activity during this time was not raised (median 3·6 U/l (range 2·2 to 10·6)) but the MB2/MB1 ratios increased (median 2·4, range 1·0 to 6·6), compared with no rejection (median 1·2, range 0·3 to 2·3, $p < 0{\cdot}003$, Mann-Whitney U test). Moreover, the MB2/MB1 ratio had increased before histological changes seen on biopsy in 6/9 patients (mean 10 days), indicating that either myocardial cell injury was present but had been missed by biopsy, or was developing before histological changes were apparent.

Total CK-MB isoenzyme activity is not raised during allograft rejection, but the MB2/MB1 ratio is significantly increased, suggesting that its measurement as a predictive non-invasive marker of allograft rejection warrants further evaluation.

Effects of physical training on skeletal muscle metabolism in chronic heart failure: experimental and human study

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Muscle deconditioning has been considered one of the possible mechanisms for the intrinsic skeletal muscle metabolic changes in chronic heart failure (CHF). To investigate the effects of physical training on the skeletal muscle metabolism we studied 12 patients (human study, HS) with ischaemic stable CHF and 32 female Wistar rats (experimental study, ES) after coronary artery ligation ($n = 22$) or sham operation ($n = 10$). Six weeks after the operation infarcted rats were allocated randomly to either another 6 weeks of training on a treadmill (T, $n = 11$) or non-training (NT, $n = 11$). Muscle pH, inorganic phosphate (Pi), phosphocreatine (PCr) utilisation, and ADP levels were evaluated before and after 8 weeks of home based bicycle exercise training in patients in a crossover randomised order and 12 weeks after the operation in both infarcted and sham operated rats. Serial ^{31}P spectra of the calf muscle were obtained at rest, throughout plantar flexion at incremental workloads until exhaustion and during the recovery period (HS) and during sciatic nerve stimulation (1 Hz) at both supramaximal and 200 g tension (ES). Rats were divided into congestive (C) and non-congestive (NC) groups according to lung/body weight ratio and enzymatic assays were performed in the contralateral leg to measure glutamate pyruvate transferase (GPT) and the mitochondrial oxidative enzymes citrate synthase (CS) and β-hydroxyacyl CoA dehydrogenase (BOAC).

Training produced an increase ($p < 0{\cdot}002$) in incremental plantar flexion exercise time. PCr utilisation and ADP levels during exercise were reduced significantly ($p < 0{\cdot}003$, ANOVA for repeated measures) by training at all matched submaximal workloads and at peak exercise. The PCr and ADP recovery half times were significantly faster after training ($p < 0{\cdot}05$). Compared with all other groups the NT C rats produced more acid at 200 g ($p < 0{\cdot}05$, ANOVA) and at maximal tension ($p < 0{\cdot}01$) and had lower PCr at 200 g ($p < 0{\cdot}01$). The NT C group had significantly lower CS in skeletal muscle than the T C or T NC and sham groups ($p < 0{\cdot}001$). There was a significant increase in GPT in the training group compared with the non-training group ($p < 0{\cdot}03$). There were no differences in BOAC.

I conclude that (*a*) skeletal muscle metabolic abnormalities in CHF depend on both congestive failure and physical deconditioning and (*b*) physical training can reverse the excessive PCr depletion and reduce ADP levels during exercise and can accelerate the rate of PCr resynthesis and ADP disappearance during recovery, indicating an improvement in the impaired oxidative metabolism of skeletal muscle seen in CHF.

Measurement of renal blood flow by continuous renal vein thermodilution: a new technique for the investigation of human cardiovascular reflexes

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This study tested the hypothesis that cutting the cardiac ventricular afferent nerve fibres at heart transplantation results in abnormal cardiovascular reflex responses to exercise in heart transplant recipients. In animals the regulatory effects of the cardiac afferent fibres exert their primary influence on the renal circulation. A continuous thermodilution technique applied in the left renal vein was developed and validated. This allowed rapid measurements of changes in renal blood flow to be made in 30 subjects (10 heart transplant recipients, 10 patients with NYHA class II heart failure, and 10 control subjects) during exercise. Measurements by the thermodilution technique correlated well with absolute blood flow in an in vitro model for blood flows ranging from 55 to 885 ml/min ($r = 0{\cdot}99$), with renal arterial blood flow measured by electromagnetic flow probe in a pig model ($r = 0{\cdot}92$), and with simultaneous measurements of renal blood flow by corrected iodohippurate clearance in humans ($r = 0{\cdot}8$). The percentage fall in renal blood flow at peak exercise was significantly greater in heart transplant recipients than in controls (45 (5)% *v* 32 (4)% $p < 0{\cdot}05$), as was the percentage increase in renal vascular resistance (transplants 116 (19)% *v* controls 78 (17)%, $p < 0{\cdot}05$). Renal haemodynamics during exercise in the heart failure group were not significantly different from those in controls.

Continuous renal vein thermodilution is a useful technique for the investigation of human cardiovascular reflexes. Ventricular cardiac denervation resulting from heart transplantation alters cardiovascular reflexes during exercise, resulting in increased vasoconstrictor drive to the kidneys. This mechanism may contribute to renal impairment after heart transplantation.

Gap junctions in normal, ischaemic and hypertrophied human ventricular myocardium: a quantitative and descriptive study of gap junction intercellular communication pathways

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Antibodies raised to a portion of the cardiac gap-junctional protein were used in an immunohistochemical procedure in combination with laser scanning confocal microscopy to localise gap junctions with a clarity not previously possible through thick volumes of human myocardium. To explore the structural basis for electromechanical dysfunction in myocardial ischaemia, infarction, and hypertrophy this technique was applied to study the organisation of gap junctions in ventricular myocardial samples obtained during surgery. Gap junctions in normal human working left ventricular myocardium are confined to the intercalated discs, with a gap-junctional surface density of 0·00508 $\mu m^2/\mu m^3$ myocardial volume. The right ventricle has similar characteristics. The border zones of healed myocardial infarcts have a considerably disturbed gap junction distribution. There is a reduced gap junction surface density in ischaemic ventricular myocardium ($p = 0{\cdot}02$) and in hypertrophy ($p = 0{\cdot}05$). When the larger cell volume of these pathological tissues is taken into account gap-junctional content *per cell* shows a significantly reduced value only when ischaemic ventricle is compared with normal ventricle ($p = 0{\cdot}02$), suggesting that the reduced surface density is a feature of ischaemia, and not simply hypertrophy, in the ischaemic heart.

These disturbances of the gap-junctional organisation may account for abnormalities of impulse propagation in ischaemic and hypertrophied ventricular myocardium and may contribute to arrhythmic tendency and mechanical inefficiency.

Clinical applications of molecular genetic analysis in familial hypertrophic cardiomyopathy

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Familial hypertrophic cardiomyopathy (FHC) in two families has been shown to be caused by cardiac myosin heavy chain (MHC) gene missense mutations. However, the disease is genetically and clinically heterogeneous and neither the fraction of FHC caused by myosin mutations nor accurate indicators of disease prognosis have been identified. To address these issues a technique incorporating the polymerase chain reaction and RNase protection assays was developed for screening the β MHC gene for mutations. Twenty four probands from unrelated families with FHC were studied. Seven β cardiac MHC gene mutations that cause FHC in 11 families were identified. All were missense mutations clustered in the head and head/rod junction of the molecule; six mutations involved a change in charge of the altered residue. In affected individuals specific mutations were associated with significantly different life expectancy. In the individuals with the two most severe mutations the mean age at death was 33 years. The one mutation that did not affect the charge was associated with near normal survival.

This new technique makes a genetic diagnosis possible in approximately 50% of families with FHC, regardless of family size. Definition of the disease-causing mutation allows preclinical diagnosis and provides important prognostic information.

Similar prevalence of enterovirus genome within the myocardium of patients with idiopathic dilated cardiomyopathy and controls shown by the polymerase chain reaction

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Enteroviral infection remains an important hypothesis for the pathogenesis of idiopathic dilated cardiomyopathy. Recent studies have suggested that with highly sensitive and enteroviral-specific techniques enteroviral genome can be detected within the myocardium of 10 to 20% patients with idiopathic dilated cardiomyopathy: however, these studies have failed to provide adequate control data. In this study we used an enteroviral-specific gene amplification polymerase chain reaction technique to detect enteroviral genome within the myocardium taken from 50 patients with dilated cardiomyopathy, 41 with other forms of heart disease, and 34 from coroners' necropsy cases. Enteroviral genome was detected in 6/50 (12%) patients with dilated cardiomyopathy and 13/75 (17%) of the controls (NS). No differences were found in dilated cardiomyopathy patients with or without myocardial enteroviral genome in respect of age, duration of symptoms, proportion of patients with a premorbid acute viral illness, excess alcohol consumption, New York Heart Association functional class, measures of left ventricular function, or endomyocardial histology. Within the control group enteroviral genome was detected in 3/15 (20%) patients with ischaemic heart disease, 2/19 (10·5%) with valvar heart disease, 1/5 (20%) with specific heart muscle disease, 0/2 (0%) with congenital heart disease, and 7/34 (20·6%) cases of sudden death. During 2 to 52 month follow up (mean 22) 15/44 (34%) patients without myocardial enteroviral genome and 2/6 (33%) with myocardial enteroviral genome died suddently or required orthotopic heart transplantation for progressive heart failure.

Enteroviral genome was detected within the myocardium in a similar proportion of patients with idiopathic dilated cardiomyopathy and controls. This finding does not support the hypothesis that persistent enteroviral infection is of pathogenic or prognostic importance in dilated cardiomyopathy but is most consistent with enterovirus being a common environmental pathogen.

Mis-sense mutations in myosin suggest a pathogenetic mechanism in familial hypertrophic cardiomyopathy

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Cardiac myosin heavy chain (MHC) gene mutations have been implicated as the cause of familial hypertrophic cardiomyopathy (FHC), but neither the types of cardiac MHC mutations that can cause FHC, nor the mechanism by which these mutations cause disease, has been defined. Previously identified cardiac MHC gene mutations suggest very different mechanisms by which altered MHC polypeptides produce this disease. Affected persons in two families have a mis-sense mutation in a highly conserved residue of the β cardiac MHC gene while affected individuals in another family have an α/β cardiac MHC hybrid gene. We have now systematically screened the β cardiac MHC genes of 24 unrelated individuals with FHC and identified seven β cardiac MHC gene mutations that cause FHC in 11 of the families. All seven of these mutations are mis-sense mutations in the head or head and rod junction regions of β cardiac MHC. Moreover, affected persons with the previously identified α/β hybrid MHC gene were found to have a coexistent mis-sense mutation that is itself responsible for FHC. Six of the seven mutations involve a charge change in the encoded amino acid and so are particularly likely to cause regional conformational change in the polypeptide. The identification of multiple new FHC-causing mis-sense mutations clustered within the MHC polypeptide suggests that mutationally altered MHC peptides act as "poison polypeptides." Analogous mis-sense mutations in a nematode MHC gene are known to produce a dominant phenotype of paralysis by incorporation of mutant heavy chains into assembling thick filaments which then disrupt sarcomere assembly. The presence of multiple different mis-sense mutations in the β MHC gene suggests a relatively high mutational rate, such that most FHC may be attributable to relatively recent mutations, rather than to a founder effect. This is in keeping with the significant premature mortality in FHC, which will tend to remove disease-causing mutations from the population, whereas new mutations account for the persistence of FHC.

A high incidence of de novo myosin mutation may account for some of the apparently sporadic hypertrophic cardiomyopathy found in people with no known affected relatives.

Myocardial nitric oxide production could contribute to cardiac depression in endotoxaemia and allograft rejection

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Endothelium derived relaxing factor (EDRF or nitric oxide (NO), produced by constitutive NO synthase) released from endocardial endothelium in isolated cardiac preparations raises myocardial cyclic guanosine monophosphate concentrations (GMP) and shorten contractile twitch duration without major effect on early systolic parameters, for example unloaded shortening velocity (V_{max}). A different, calcium independent NO synthase enzyme inducible by cytokines, for example interleukin-1β (IL-1), has recently been isolated in mammalian myocytes. The effects of IL-1 on contraction and cyclic GMP content in isolated ferret papillary muscles ($n = 33$; with 1 μM acebutolol and 10 μM indomethacin) were therefore studied. After three hours incubation, IL-1 (10 ng/ml) reduced time to peak isometric tension (tPT) by 14·0 (3·0)% (mean (SE) and peak tension (PT) by 6·9 (1·6)%, and increased cyclic GMP by 95·8% ($p < 0·05$; $n = 6$), without altering V_{max}. These effects were independent of the endocardium. The contractile effects of IL-1 were inhibited (tPT −3·5 (2·0)% and −3·7 (1·4)% respectively (NS; $n > 6$)) in the presence of L-N^G-monomethylarginine (L-NMMA (50 μM) for 30 min) or dexamethasone ((3 μM) for 3 hours), which both inhibit inducible NO synthase. The IL-1 induced increase in cyclic GMP was 10·4% ($n = 6$) in the presence of L-NMMA and 52·1% ($n = 6$, $p < 0·05$) in the presence of dexamethasone.

Thus IL-1, probably by inducing myocardial NO synthase, mimics the characteristic EDRF effect of shortening the duration of myocardial contraction, which could reduce stroke volume and contribute to cardiac depression in immune mediated shock, for example, endotoxaemia and allograft rejection.

Beneficial effects of growth hormone replacement therapy on myocardial function

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Patients with hypopituitarism who have replacement therapy with thyroxine and adrenal steroids but not growth hormone have increased cardiovascular mortality. A recent report has found that a substantial number of these patients have impaired myocardial function, in particular a reduced exercise time, electrocardiographic abnormalities on exercise, and abnormal left ventricular diastolic function. To assess whether growth hormone replacement therapy (0·06 IU/kg of body weight given subcutaneously once daily) improves these abnormalities, we conducted a double blind, placebo controlled study on 26 adults with hypopituitarism for six months (12 men, 14 women; mean age 45 (12) years). Cardiac structure and function were assessed with cross sectional echocardiography and Doppler ultrasound, and treadmill exercise tolerance was assessed with the Bruce protocol. During the six month study period there were no changes in left ventricular mass index in either the placebo group (88 (18) g/m^2 at baseline, 92 (14) g/m^2 at six months) or the growth hormone treated group (96 (21) g/m^2 and 94 (22) g/m^2). Of the indices of left ventricular diastolic function, isovolumic relaxation time improved in the growth hormone treated group (102 (15) ms at baseline, 92 (11) ms at six months, $p < 0·05$) but not in the placebo group (99 (17) ms and 93 (13) ms, $p > 0·03$). No difference was found in the indices of left ventricular filling (E:A ratio) in either group. Exercise duration increased in the growth hormone treated group (8·4 (1·9) min at baseline, 9·4 (1·5) min at six months, $p < 0·04$) but not in the placebo group (8·7 (4·4) min and 8·7 (4·1) min, $p > 0·9$). No change was found in the rate-pressure product in either group after six months. Four patients in the growth hormone treated group and three in the placebo group developed planar ST depression > 0·1 mV during exercise testing at baseline which did not change in either group after six months.

These findings suggest that growth hormone replacement therapy even over a short period of time has several potentially beneficial cardiac effects in patients with hypopitituitarism and may possibly in the long-term reduce their increased cardiovascular mortality.

Effects of type 1 diabetes on left ventricular size and function: Doppler echocardiographic study of identical twins

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Heart failure occurs more frequently in diabetic than non-diabetic patients despite a similar extent of coronary artery disease, suggesting the presence of a specific diabetic heart disease. In order to elucidate the nature of this heart disease previously described in heterogeneous populations of diabetics, we assessed left ventricular size and function by 2D-Doppler echocardiography in 36 young (mean 26, range 10 to 37 years) normotensive identical twin pairs discordant for type 1 diabetes (mean duration 14 years). End diastolic volume (EDV), end systolic volume (ESV) and left ventricular mass were calculated from echo images and indexed. Diastolic function was measured as: the ratio of transmitral blood flow velocities during early and late left ventricular filling (E/A), time-velocity integrals of early (E integral) and late (A integral) left ventricular filling, and percentage of diastolic filling contributed by atrial systole (A%). Diabetic twins, compared with non-diabetic twins, had lower EDV and ESV (72 (20) *v* 76 (19) ml/m^2, $p < 0\cdot001$ and 31 (8) *v* 36 (14) ml/m^2, $p < 0\cdot02$) and lower E/A ratio (1·4 (0·3) *v* 1·6 (0·3), $p < 0\cdot0005$). Although the total time-velocity integrals of diastolic filling were similar between the twins, the diabetic twins had higher A integral (55 (18) *v* 47 (10), $p < 0\cdot005$) and higher A% (32 (5) *v* 29 (5))%, $p < 0\cdot005$). Left ventricular mass, stroke volume, and relative wall thickness were similar between diabetic and non-diabetic twins. The smaller left ventricular size and altered left ventricular diastolic function in the diabetic twins were not causally related to disease duration, microvascular complications, or glycaemic control.

Young normotensive type 1 diabetics have decreased left ventricular chamber volume and subclinical diastolic dysfunction but retain normal systolic function, consistent with the existence of a specific diabetic heart disease.

The duration and nature of isovolumic relaxation determine the Doppler A/E ratio in left ventricular disease

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It is widely recognised that loading conditions, age, and heart rate influence peak mitral flow velocity and the Doppler A/E ratio. To assess possible additional effects of abnormal relaxation, we examined left ventricular (LV) filling with Doppler and M mode echocardiography in 47 patients with ischaemic heart disease (IHD), 35 with LV hypertrophy (LVH), and in 26 normal people. We digitised M modes and measured incoordinate relaxation as % change in LV dimension before mitral valve opening, isovolumic relaxation time (IVRT), and rates of LV dimension increase and posterior wall thinning. Left ventricular end diastolic pressure was measured at cardiac catheterisation. The A/E correlated with age in normal subjects ($r = 0\cdot74$), to a lesser extent in LVH ($r = 0\cdot41$), but not significantly in IHD. In LVH and those patients with ischaemic heart disease without LV dilatation, A/E was correlated both with IVRT ($r = 0\cdot67$ and 0·68 respectively), and with incoordinate relaxation ($r = 0\cdot64$ and 0·58). In those ischaemic heart disease patients with LV dilatation (end diastolic dimension > 6 cm), the influence of incoordination was lost and IVRT became the dominant influence upon A/E ($r = 0\cdot83$) (all p values $< 0\cdot01$). This was despite considerable incoordinate relaxation being evident in this subgroup. Stepwise regression confirmed that weak correlations of LV end diastolic pressure and RR interval with A/E became insignificant once IVRT had been taken into account. In 16 patients who had two examinations on different occasions, changes in IVRT were matched by changes in A/E, predicted by the relation derived from the group as a whole.

The influence of filling pressure and RR interval on A/E in patients with LV disease acts through an effect on IVRT. Age is an important influence in normal people, but this effect is attenuated in LVH and lost in IHD. Thus the filling pattern is effectively determined before mitral valve opening from two discrete properties of IVRT: its duration, and degree of incoordination during it, when cavity size is normal.

Breathlessness in microvascular angina

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In patients with microvascular angina, there is some evidence from studies of plethysmography, of widespread microvascular abnormalities. As well as exertional chest pain, all of these patients complain of breathlessness, with no evidence of airways obstruction or resting left ventricular dysfunction. Progressive exercise testing was performed in 11 age and sex matched controls and 11 patients (two men), in whom the diagnosis of microvascular angina was established on the basis of exertional chest pain, abnormal thallium scans, and an attenuated myocardial flow response to a vasodilator challenge, with angiographically entirely normal epicardial vessels. Symptom limited exercise was performed with on line ventilation and expired gas analysis, measuring minute by minute ventilation, oxygen consumption and carbon dioxide production, and arterial blood gas values, using a transcutaneous system. Anaerobic threshold was calculated by curve fitting a plot of oxygen consumption against carbon dioxide production. Compared with controls 49·73 SD (7·3) in patients with microvascular angina, anaerobic threshold was 41·55 (5·82), $p < 0\cdot016$ (% predicted Vo_{cmax}) but still within normal limits. Maximal oxygen consumptions, as percentage of predicted, was reduced 59·73 (16·51) compared with 86·55 (4·91)%, $p < 0\cdot003$ and the mean ventilatory response VE/Vco_2 was significantly increased 35·20 (8·01) *v* 26·49 (3·08) (l/lCO_2 output), $p < 0\cdot016$.

These results suggest that in patients with microvascular angina on maximal exercise there is significant "wasted ventilation," consistent with areas of the lung being underperfused and accounting for the sensation of breathlessness.

Coronary arterial endothelium dependent vasodilator responses in syndrome X

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Certain features in patients with syndrome X (SX)—namely, chest pain, positive exercise test, and angiographically normal coronary arteries—are suggestive of transient myocardial ischaemia. A functional abnormality at the level of the resistance vessels, possibly due to impaired endothelium dependent vasodilatation, may explain the syndrome. With an intracoronary Doppler probe to measure coronary blood velocity and quantitative angiography to determine coronary artery diameter, endothelium dependent responses to acetylcholine (ACh) and substance P (SP) were assessed in 10 SX patients and nine controls (atypical chest pain, negative exercise test, and angiographically normal epicardial coronary arteries). Intracoronary infusions of ACh (10^{-7} M and 10^{-6} M) and SP (5, 10, and 25 pmol/min) were given. Flow (area × velocity) was determined before infusion and at peak response to produce a flow ratio (peak:baseline flow). Epicardial area was not significantly altered by ACh, but was increased with SP by (mean (SEM)) 51·2 (17·3)% (in the SX patients, $p < 0·05$), and 53·1 (7·3)% (in the controls, $p < 0·05$). Flow ratios were greater with ACh (2·71 (0·32 in the SX patients, $p < 0·01$) and 2·88 (0·42) (in the controls, $p < 0·05$)) than with SP (1·88 (0·13) (in the SX patients, $p < 0·05$) and 2·42 (0·43) (in the controls, $p < 0·05$)). There was no significant difference between SX patients and controls with either drug.

Endothelium dependent vasodilator responses are not impaired in SX patients compared with a control group, and this highlights the different effects of ACh and SP on the coronary bed. If a functional abnormality exists then other mechanisms must be considered.

Effect of hyperventilation and mental stress on coronary blood flow in patients with syndrome X

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The mechanism of chest pain in patients who present with chest pain, a positive exercise test, and normal coronary arteries (syndrome X) is not clear. Syndrome X is a heterogeneous disorder and the various proposed theories include abnormalities of coronary vasodilator reserve in some patients whereas psychological, hyperventilation, and oesophageal factors have been reported in others. We investigated the effect of hyperventilation and mental arithmetic stress in a group of 18 syndrome X patients. All cardiac medications were stopped 48 hours before the tests. All patients first underwent hyperventilation and mental stress test on the ward 24 hours before the cardiac catheter. With a standard femoral approach a 3·6 F intracoronary Doppler catheter (Schneider, UK) was positioned in the proximal left anterior descending coronary artery. The resting coronary blood flow velocity was measured with the patient in the supine position and breathing normally. Hyperventilation followed by mental arithmetic stress test was performed in the first 10 patients and the order was reversed in the remaining eight. During the tests performed on the ward, 10 patients experienced their usual chest pain on hyperventilation and 10 patients during or soon after the mental stress test but none of these episodes produced appreciable ischaemic electrocardiographic changes. Seven of the 10 patients in both groups experienced chest pain with both hyperventilation and mental stress. This exact pattern was repeated during the cardiac catheter with hyperventilation and mental stress. Hyperventilation produced a significant increase in heart rate (77 (SD) (17) *v* 85 (16) $p = 0·001$) but no significant change in systolic blood pressure. The rate-pressure product increased significantly from 9267 (2216) to 10 528 (3045) ($p = 0·009$). Coronary blood flow velocity, however, decreased significantly from 7·6 (4·9) cm/s to 6·6 (5) cm/s ($p = 0·02$, paired *t* test). On mental stress test there was no significant difference in heart rate (78 (16) *v* 80 (16)), systolic blood pressure (132 (24) *v* 135 (26)), or coronary blood flow velocity (8·3 (5·2) *v* 7·4 (4·5)).

In syndrome X patients although both hyperventilation and mental stress can produce chest pain, only hyperventilation appears to significantly reduce coronary blood flow.

Effects of hormone deficiency on cardiovascular risk markers in women

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Loss of ovarian function increases the incidence of cardiovascular disease in women. The effects, however, of gonadal steroid deficiency and replacement are not fully understood. One mechanism of action may be through changes in lipids and lipoproteins. In a cross sectional study of 553 healthy women with clearly defined menopausal state, we measured fasting lipids and lipoproteins. There was an age related increase in total cholesterol, triglyceride, low density lipoprotein (LDL) cholesterol, and high density lipoprotein subfraction 3 (HDL_3) cholesterol, and a decrease in high density lipoprotein subfraction 2 (HDL_2) cholesterol concentrations. There was also an independent increase in total cholesterol, triglyceride, and LDL cholesterol, and a decrease in HDL_2 cholesterol concentration associated with the menopause. Thus loss of ovarian function appears to adversely affect lipids and lipoproteins. This may be mediated in part through changes in body fat distribution. We have previously shown that android fat correlates positively with triglyceride and LDL cholesterol, and negatively with HDL and HDL_2 cholesterol concentrations. We have now measured regional body fat mass by dual energy *x* ray absorptiometry in 131 healthy non-obese women. We found that total fat mass is higher in postmenopausal than in premenopausal women ($p < 0·01$), but there is also a significantly greater proportion of android (upper body segment) fat ($p < 0·001$) with a lesser proportion of gynoid (lower body segment) fat ($p < 0·001$). This redistribution of body fat would be in keeping with the adverse lipid changes found.

Thus loss of ovarian function at the menopause is associated with adverse changes in body fat distribution and lipids and lipoproteins. These changes in risk markers may in part explain the increased incidence of cardiovascular disease in postmenopausal women.

Non-invasive monitoring of rejection: soluble interleukin-2 receptor concentrations may predict subsequent acute allograft rejection in the transplanted heart

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We have shown that endothelial major histocompatibility complex class II expression in endomyocardial biopsies predicts subsequent significant acute cardiac rejection with cellular infiltration and myocytolysis. Activation of T cells is accompanied by the elaboration of Interleukin-2 and its subsequent binding to a specific receptor complex (sIL2R). Monoclonal antibodies to sIL2R have been developed as anti-rejection agents. Studies in humans have so far failed to show a correlation between sIL2R and rejection, perhaps because of coincident infection, or liver or renal dysfunction. We analysed sIL2R concentrations at the time of biopsies, and excluded these aforementioned cases, to see if clinically significant rejection could still be predicted. Two hundred and thirty biopsies and concurrent sIL2R concentrations were obtained from 33 orthotopic heart transplant recipients in their first six postoperative months who were treated with cyclosporin, azathioprine, and prednisolone (the last was stopped after three months). Concentrations of sIL2R during acute infection, cholestasis (bilirubin $>25\,\mu$mol/l), or a serum creatinine $>350\,\mu$mol/l were excluded for 98 samples. Nineteen episodes of acute rejection occurred in 18 patients. Whereas the sIL2R concentration was moderately related to the concurrent degree of rejection (ANOVA, $p = 0{\cdot}02$, regression $p = 0{\cdot}005$), it was more strongly related to the degree of rejection that developed 1 to 6 weeks later (ANOVA, $p = 0{\cdot}003$, regression $p = 0{\cdot}0008$). Expressed as a percentage change from the initial sIL2R concentration taken at the first postoperative biopsy, sIL2R strongly predicted the appearance of acute rejection one to six weeks later (regression $p = 0{\cdot}0001$).

This shows that rising sIL2R concentrations are part of a non-specific immune activation process, but may have a potential role as a predictor of clinically significant rejection in the absence of infection, cholestasis, or severe renal dysfunction.

Differences in the fatty acid composition within human aortic plaques

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The fissuring of an atherosclerotic plaque may be a crucial event in the onset of acute myocardial infarction. The lipid composition of these complex lesions may in part determine why some plaques fissure and others remain intact. Analysis of samples from 57 non-ulcerated plaques indicated no significant difference in total saturated, monounsaturated, or polyunsaturated fatty acids between the centre and edges of these lesions. At the edge of 25 ulcerated plaques we found significant increases in the proportions of stearate, dihomo-γ-linolenate, arachidonate, and docosahexadecanoate. There was an overall increase in saturated fatty acids ($p < 0{\cdot}001$) and a decrease in n-6 polyunsaturated fatty acids ($p < 0{\cdot}001$). In all plaques, the ratio of polyunsaturated:saturated fatty acids was lower at the edge compared with the centre. The fatty acids at the edge and in the centre of all plaques contained roughly 40% polyunsaturated and 35% monounsaturated fatty acids. The composition of unsaturated fatty acids in non-ulcerated plaques was similar to that seen in plasma. In ulcerated plaques, however, this similarity between plaque and serum fatty acids only held for n-3 polyunsaturated fatty acids.

Factors such as high concentrations of relatively unstable polyunsaturated fatty acids at the periphery of advanced plaques (an area subject to considerable haemodynamic stress) and the potential formation of hydroperoxy derivatives of polyunsaturated fatty acids may help explain the prevalence of fissures at the edge of atheromatous plaques.

Improved cerebral protection with alpha-stat acid base regulation after coronary artery bypass surgery

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It is well recognised that after coronary artery bypass surgery a variable degree of postoperative cerebrocortical dysfunction occurs. It seems likely that many of the imperfections and alterations in cerebral blood flow (CBF) during cardiopulmonary bypass (CPB) may be due to changes induced by altered acid-base management of the patient during CPB. Seventy patients undergoing elective coronary artery bypass surgery were randomised to undergo surgery using one of two differing, but widely practised, CPB acid base protocols; that of alpha-stat and pH-stat. CBF was measured during surgery using xenon-133 isotope clearance technique. Cerebral oxygen metabolism was measured as the cerebral metabolic rate for oxygen ($CMRO_2$) and matching of cerebral blood flow to oxygen demand by the brain as the cerebral extraction ratio for oxygen ($CERO_2$). The patients were investigated at six weeks after surgery for changes in neuropsychological function. During hypothermic (28°C) CPB, cerebral blood flow was significantly ($p < 0{\cdot}001$) greater in the pH-stat group ($41\,ml^{-1}\,100\,g^{-1}\,min^{-1}$; 95% CI 39 to 43) than the alpha-stat group ($24\,ml^{-1}\,100\,g^{-1}\,min^{-1}$; 95% CI 22 to 26). The values for the $CERO_2$ indicated a degree of mismatch of cerebral perfusion and demand during CPB in both alpha and pH-stat groups (0·25, 95% CI 0·22 to 0·28 and 0·12, 95% CI 0·11 to 0·14 respectively). This mismatch was far more pronounced in the pH-stat group than the alpha-stat group, indicative of a greater degree of disruption in cerebral autoregulation in the pH-stat group. Neuropsychological assessment showed a significantly (Fisher's exact test, $p = 0{\cdot}02$) higher proportion faring less well at six weeks in the pH-stat group than in the alpha-stat group (17/35, 48·6%; 95% CI 32 to 65·1%, and 7/35, 20%; 95% CI 6·7 to 33·2% respectively).

The alpha-stat managed group displayed less disruption of cerebral autoregulation during cardiac surgery than the pH-stat group. This was accompanied by a reduction in the incidence of postoperative cerebral dysfunction. This study has shown that acid base management is an important consideration during cardiopulmonary bypass in terms of cerebral impairment after coronary artery bypass surgery.

Inhibition of thrombus formation in vivo by urokinase linked to a monoclonal antibody which recognises damaged endothelium

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Saphenous vein grafts are subject to early thrombotic occlusion, a process related to endothelial injury incurred during vein harvesting. A monoclonal antibody (P14G11) that binds to damaged endothelial cells has been linked to urokinase. This conjugate was investigated in vivo. Wistar rats were anaesthetised, a 2 cm segment of vena cava dissected free, and the endothelium damaged by clamping for five minutes. Test substances were introduced for 15 minutes. After 30 minutes the cava was opened and the thrombus weighed. Test substances were saline (control), urokinase (200 IU/ml), IgG-urokinase conjugate (200 IU/ml), and P14G11 antibody-urokinase conjugate (200 IU/ml). Mean weights of thrombus (mg (SE)) were: group 1, control (n = 8) 17·6 (2·8); P14G11-urokinase (n = 8) 4·2 (1·2); urokinase (n = 8) 16·3 (3·7). Group 2: control (n = 7) 14·4 (3·8); IgG-urokinase (n = 7) 16·1 (4·7). The P14G11 conjugate reduced thrombus formation *v* control and urokinase groups (p < 0·02 (Wilcoxon test)). No difference was found between the IgG conjugate and control groups.

The P14G11 conjugate may have a role in preventing local thrombosis in vein grafts after coronary artery bypass grafting.

Pacing thresholds of epicardial electrodes

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Failure of epicardial wires after cardiac surgery is potentially hazardous. We compared the variation of pacing thresholds in 60 patients using two commercially available pacing wires at different epicardial sites after coronary surgery with either cardioplegia or ventricular fibrillation. In 30 patients a bare, braided pacing wire (DW) was placed on the right ventricle and a medtronic localised epicardial electrode (MW) on each ventricle. In another 30 patients the DW wire was placed on the right atrium and an MW electrode was placed on each atrium. Pacing thresholds were measured at the time of placement, and at one, six, and 12 hours and daily for five days. The pacing thresholds at implantation were (mean volts (SD)) MW 0·65 (0·48) and DW 1·28 (1·0), in the atria and MW 0·63 (0·53) and DW 0·93 (0·45) in the ventricles. On the fourth postoperative day the pacing thresholds were MW 1·04 (0·49) and DW 2·33 (1·57) in the atria and MW 1·19 (1·21) and DW 2·08 (1·15) in the ventricles. These changes in pacing thresholds were analysed by repeated measures analysis of variance which confirmed that the thresholds of both types of wire increased significantly with time (p < 0·001), but this deterioration was more pronounced with the braided wire both on the atrium (p < 0·005) and the ventricle (p < 0·05). The pacing threshold patterns were not affected by chamber side (left or right) or mode of myocardial preservation. The braided ventricular wire failed to capture after 24 hours in 9/30 patients whereas the epicardial electrode captured in all instances (p < 0·001). There was no significant difference in failure rate between the two wires in the atrial position.

Localised epicardial electrodes have consistently lower pacing thresholds than the braided wires on both the atria and ventricles and are less prone to failure on the ventricles.

Early experience with intravenous oxygenation

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We have used intravenous oxygenation in eight patients (four men) with acute respiratory failure (acute respiratory distress syndrome four, pneumonia three, and fibrosing alveolitis one). Their median age was 39 (range 14 to 76). At the time of referral for intravenous oxygenation all patients were on inotropic support, five had pneumothoraces and two were on haemofiltration. Ventilatory data were: ventilated for 2 to 14 days (median six), FiO_2 70 to 100% (100), positive inspired pressure 34 to 95 cm H_2O (49), positive end expiratory pressure 5 to 15 cm H_2O (12), minute volume 7 to 29 dl/kg min (15), PaO_2 5·4 to 26 KPa (8·5), and $PaCO_2$ 3·7 to 23 KPa (8). The device was inserted via the femoral vein and positioned in the right atrium and both venae cavae. Intravenous oxygenation was used for six hours on 12 days (4), the O_2 transfer achieved was 68 to 140 ml/min (85) and the CO_2 removed was 40 to 106 ml/min (59). It was possible to decrease the ventilator settings with a significant increase in the PaO_2 by 48 hours (p < 0·05 by analysis of variance) but the fall in PaO_2 did not reach significance. Two patients survived and six died from multisystem failure with three being hypoxic at the time of death. Five patients had post mortem examinations and no complications related to intravenous oxygenation occurred.

Intravenous oxygenation is not at present as efficient as extra corporeal membrane oxygenation but does not have the detrimental effects on the mechanisms of coagulation that preclude the use of extra corporeal membrane oxygenation for more than a few days.

Effect of continuous warm blood cardioplegia versus crystalloid cardioplegia in the isolated blood perfused rat heart

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Continous warm blood cardioplegia (CWBC), by avoiding hypothermia and ischaemia, has been suggested to improve the protection of myocardium during cardiac surgery. With the isolated blood perfused rat heart, we compared the protective effects of CWBC with those of continuous warm (37°C) crystalloid cardioplegia and the hypothermic (20°C) multidose crystalloid cardioplegia. Three groups of heart (n = 6/group) were arrested with: (*a*) CWBC (mixture of rat blood with Fremes' solution in a ratio of 4:1) infused at 37°C at the rate of 0·8 ml/min throughout the period of arrest; (*b*) multidose St Thomas's cardioplegic solution No 1 infused at 20°C every 30 min for two min; and (*c*) continuous warm (37°C), glucose enriched, crystalloid cardioplegic solution (mixture of Krebs' buffer with Fremes' solution in a ratio of 4:1) infused at

0·8 ml/min. After three hours of arrest, the hearts were reperfused at 37°C with arterial blood from a support rat at a constant flow rate of 2·5 ml/min. After 40 min of reperfusion, the perfusion pressure (an index of coronary resistance) was 60 (6), 50 (5), and 88 (9) mm Hg in groups (*a*), (*b*) and (*c*) respectively. The left ventricular developed pressure (LVDP) and end diastolic pressure (LVEDP) were assessed at a range of left ventricular volumes (30 to 300 μl) with an intraventricular balloon. At a ventricular volume of 210 μl, the LVDP was 104 (5), 74 (3), and 64 (7) mm Hg in groups (*a*), (*b*), and (*c*) respectively; and the LVEDP was 18 (3), 9 (2), and 33 (7) mm Hg, respectively. These results indicated that CWBC provided a greater protection of systolic function than the other two groups. The ventricular compliance was best preserved in hearts receiving hyperthermic St Thomas's Hospital cardioplegic solution No 1.

The worst preservation of ventricular compliance and coronary vasculature were seen in the heart receiving continuous warm crystalloid cardioplegia.

Role of internal thoracic artery in patients undergoing urgent and semi-urgent surgery for complete coronary revascularisation

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Ninety eight patients aged 29 to 86 (mean 58) underwent coronary artery bypass grafting on an urgent or semi-urgent basis for unstable angina (64·3%), evolving infarction (19·4%), critical left main coronary artery (LMS) stenosis (>90% narrowing) (13·3%), and failed angioplasty (3·1%); 11·2% had had previous coronary artery bypass grafting. Preoperative angiography showed significant disease (>50% narrowing) in the left main coronary (17·3%), left anterior descending (95·9%), circumflex (84·7%), and right coronary artery (82·7%); 78·8% had impaired left ventricular function (ejection fraction <50%). Of these 11% had an ejection fraction of <30%. The number of grafts ranged between one and 10 (mean six) and 90·8% had at least one internal mammary artery (of these, 32·8% had bilateral internal mammary arteries); 9·2% received vein grafts only, seven of whom were haemodynamically unstable, and in two the internal mammary arteries were unsuitable; 13·3% had an additional cardiac procedure. Early mortality was 3·1% (95% confidence intervals (0·64–8·69)) (two were cardiac related). Five had electrocardiographic evidence of perioperative infarction. All patients were reviewed at six weeks. Two had recurrent angina; 82·7% were in New York Heart Association functional class I, 12·2% in class II, and 2% in class III.

Provided patients are not in cardiogenic shock, single or bilateral internal mammary arteries with their known long term advantages can be used in patients undergoing urgent complete revascularisation with an acceptable mortality and morbidity.

Effect of propafenone and verapamil on the inward calcium current in isolated cardiac myocytes

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Propafenone is a potent class 1c agent for the treatment of supraventricular and ventricular arrhythmias. Its major action is on the fast inward sodium current with reduction of the maximal rate of depolarisation of the action potential. There is increasing evidence that slow action potentials and afterdepolarisations, both of which are dependent upon calcium entry, have important roles in arrhythmogenesis. Experiments on multicellular cardiac preparations have suggested that propafenone may block calcium currents in the myocardium. This study examines the effects of propafenone on the inward calcium current (I_{Ca}) in isolated cardiac myocytes and compares these with the classical calcium channel antagonist, verapamil. Single guinea pig ventricular cardiac myocytes were obtained by enzymatic digestion. Calcium currents were studied using the whole cell clamp method (external solution composition (mM) NaCl 112, $NaHCO_3$ 24, NaH_2PO_4 1, KCl 5·4, $MgCl_2$, 1 HEPES 5, glucose 10; pH 7·4 with NaOH: pipette solution CsCl 130, HEPES 15, $MgCl_2$ 1, Na_2ATP_2 2, EGTA 1; pH 7·2 with CsOH). Sodium currents were inhibited by a 100 ms prepulse from −80 to −40 mV and potassium currents by intracellular caesium. Known concentrations of drug were added by perfusion into the recording bath. Propafenone inhibited the I_{Ca} over 10 to 20 minutes in these myocytes. The dose response curve was measured at 10 different concentrations of propafenone from 1×10^{-8} mol/l to 1×10^{-3} mol/l (n = 3 to 11 cells (mean = 5) for each dose). The concentration of propafenone for 50% maximal block of I_{Ca} was $1·5 \times 10^{-6}$ mol/l. Propafenone did not exhibit use dependent block of the calcium current. Propafenone at concentrations of 1×10^{-6} mol/l blocked the I_{Ca} by 42·1 (4·7)% (SD) (n = 11) whereas verapamil at a dose of 1×10^{-6} mol/l blocked the I_{Ca} by 48·6 (7·7)% (n = 8). Verapamil showed both tonic and use dependent block of the I_{Ca}.

Propafenone is a powerful calcium channel blocker at clinically therapeutic concentrations of the drug; its mechanism of action, however, differs from that of verapamil.

Naloxone has non-receptor mediated Class I and Class III antiarrhythmic activity and attenuates the rate of extracellular potassium accumulation during myocardial ischaemia

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Opioid peptide release during myocardial ischaemia may contribute to early ischaemic arrhythmias. Naloxone and other opioid receptor antagonists possess antiarrhythmic activity in animal models of coronary artery occlusion but this may be due to non-receptor mediated effects rather than opioid receptor blockade. We have investigated the cardiac electrophysiological effects of naloxone in isolated myocardium from New Zealand White rabbits. In superfused papillary muscles, naloxone ($n = 7$) produced a dose-dependent parallel prolongation of action potential duration (APD) and effective refractory period (ERP), a class III effect. Mean (SEM) values were 216 (11) ms and 210 (11) ms respectively at baseline, 240 (14) ms and 232 (13) ms at 10^{-6} mol/l^{-1} ($p < 0{\cdot}001$), and 327 (8) ms and 320 (10) ms at 10^{-4} mol/l^{-1} ($p < 0{\cdot}00001$). Similar effects were seen with another opioid antagonist (nalmafene $n = 7$) and an agonist (morphine $n = 7$). Under hyperkalaemic conditions, naloxone ($n = 7$) reduced the maximum upstroke velocity of the action potential (dV/dt_{max}) and produced postrepolarisation refractoriness, a class I effect. In arterially perfused interventricular septa, both d l-naloxone (active at opioid receptors $n = 7$) and d-naloxone (inactive $n = 6$) significantly prolonged APD and ERP compared with control ($n = 7$). During global ischaemia the class III effects were gradually lost but the shortening in APD was more marked than the reduction in ERP leading to the development of postrepolarisation refractoriness. Both compounds reduced the accumulation of extracellular potassium: control 0·28 (0·01) mmol/l^{-1} min^{-1}, d l-naloxone 0·18 (0·01) mmol/l^{-1} min^{-1}, and d-naloxone 0·20 (0·02) mmol/l^{-1} min^{-1}, $p = 0{\cdot}003$. The fall in dV/dt_{max} during ischaemia was enhanced compared with control.

Attenuation of the rate of rise of extracellular potassium concentration during ischaemia and non-opioid receptor mediated cardiac electrophysiological effects may explain the antiarrhythmic activity of naloxone.

Stretch-induced electrical dispersion: evidence in humans from a new in vivo model

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Recent experimental evidence has highlighted the importance of diastolic stretch in the initiation of ventricular arrhythmias resulting from mechano-electric interaction. We have developed a model for the study of this mechanism in humans using the presence or absence of the atrial contribution to ventricular filling to alter diastolic stretch in the human left and right ventricle. Duration of monophasic action potential was measured simultaneously from the left and right ventricular endocardium as a measure of repolarisation and dispersion of repolarisation between the two regions. Seventeen patients were studied (aged to 38 to 69, median 49). After routine coronary angiography, the two monophasic action potential catheter electrodes and two pacing electrodes were positioned (right atrium and right ventricle). In a total of 34 observations, changing from steady state right ventricular pacing to atrioventricular sequential pacing (thereby incorporating the atrial contribution to ventricular filling) raised peak systolic pressure from 112 (2) (mean (SEM)) mm Hg to 142 (2). The right ventricular action potential duration changed in 27 observations ($p < 0{\cdot}02$) by up to 20 ms and the left ventricular action potential changed by a maximum of 42 ms ($n = 28$; $p < 0{\cdot}025$). The overall difference in duration of monophasic action potential between the two sites (that is, the electrical dispersion between the two regions) altered by a median of 12 ms (ranges: 0–4 ms ($n = 9$), 6–10 ($n = 6$), 12–20 ($n = 14$), 20–42 ($n = 5$)).

Our results have shown that alteration in diastolic stretch using the atrial component to ventricular filling alters duration of action potential at both right and left ventricular sites and dispersion between the two regions. Thse findings are consistent with mechano-electric feedback whereby alteration in ventricular loading (diastolic stretch) alters the duration of the action potential (and hence refractoriness). The model that we have employed is applicable to the study of stretch induced arrhythmogenic mechanisms in patients with coronary heart disease.

Clinical and haemodynamic performance of the 19 mm Carpentier-Edwards supra-annular aortic valve

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The clinical and haemodynamic performance of the 19 mm Carpentier-Edwards supra-annular aortic valve (CE-SAV) is unknown compared with the larger valves. Over four years we implanted 19 mm CE-SAV into 21 patients (20 women), mean age 75 (1·2) (range 59–86) and mean body surface area 1·6 (0·03) m^2 (range 1·3 to 1·7). There were four deaths, one at surgery and three late non-cardiac deaths. Follow up of the 17 survivors for a mean of 20 (3·1) months (range 2–42) found symptomatic improvement in all 17 (all are now in New York Heart Association functional class I and II). There were no valve related complications and no patient required long term anticoagulation. Echocardiographic and Doppler studies were used to assess the in vivo haemodynamic profile of the valve. Mean postoperative aortic valve gradient was 34·1 (2·7) mm Hg (range 19–52). Functional valve orifice area was 1·1 (0·09) cm^2 (range 0·6–1·8). Mean cardiac output was 3·92 (0·17) l/min (range 3·2–5·1) with a mean cardiac index of 2·5 (0·11) l/min/m^2 (range 2·1–3·2).

Aortic valve replacement with the 19 mm CE-SAV has a low operative mortality and offers major clinical benefits despite moderate transprosthetic gradients. This approach provides an alternative management strategy in elderly patients who would otherwise require low profile mechanical valves or aortic root enlargement.

Ambulatory pulmonary artery pressure monitoring in pulmonary hypertension: diurnal variation and effects of exercise and daily activities

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Ambulatory pulmonary monitoring was used to investigate the pulmonary haemodynamics of primary pulmonary hypertension in six patients. These patients (age 38, range 17–54) who were awaiting heart-lung transplantation underwent 24 hour ambulatory pulmonary artery pressure recordings with a micromanometer tipped catheter incorporating an in vivo calibration system, and a digital recorder. During this period patients undertook submaximum exercise walking up and down stairs, and walking on the level, and maximum exercise on a treadmill. Four of these patients underwent simultaneous non-invasive ambulatory systemic blood pressure recording. The mean 24 hour pulmonary artery pressure (mm Hg (SD)) was 101 (25)/47 (12). The mean day time pressure was 99 (24)/47 (12) and mean night time pressure was 107 (28)/50 (14). From lying to standing the pressure fell from 106 (33)/45(14) to 81(26)/37 (15·9). At peak exercise walking on the level the pressure was 127 (39)/63 (18), on the stairs 129·5 (39)/56 (16), and on the readmill 136 (35)/62 (17). Patients rated the stairs as the most severe exercise. Although pulmonary artery pressure appeared primarily to be related to the patients' activities, two patients sustained an unprovoked episode of systolic pressure exceeding 200 mm Hg lasting about one minute. Blood pressure monitoring showed that the 24 hour mean was not significantly different from pulmonary artery pressure. The mean day time blood pressure was 101 (23)/68 (16) and the mean night time pressure was 94 (16)/62 (9). At peak exercise the blood pressure walking was 85 (34)/69 (14), on the satirs 88 (34)/65 (17), and on the treadmill 95 (30)/59 (14).

Pulmonary artery pressure was at systemic level and tended to rise at night to the same level as lying during the day. Pulmonary artery pressure rose on exercise to a level at which there was no significant difference between submaximum and maximum exercise. Pulmonary artery pressure became suprasystemic at night and on exercise, and was associated with a fall in blood pressure. These findings may have implications with regard to the mechanisms involved in regulating pulmonary artery pressure in these patients as well as therapeutic implications.

Role of transoesophageal echocardiography in cardiac surgical intensive care

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Transoesophageal echocardiography (TEE) is becoming established as a valuable intraoperative procedure. Its role, however, in the cardiac surgical intensive care unit is less well defined. To investigate this we reviewed all TEE studies performed in a cardiac surgical intensive care unit over a six month period (n = 50). Indications for emergency TEE were suspected prosthetic valve dysfunction (n = 5), intracardiac source of embolism (n = 2), or aortic pathology (n = 3), unexplained postoperative hypotension/cardiac failure (n = 10), and major thoracic trauma (n = 7). TEE was only performed if precordial echocardiography had failed to give a definitive diagnosis. In 23 patients, intraoperative TEE monitoring of left ventricular function during coronary artery bypass surgery was continued electively in the intensive care unit postoperatively. In thoracic trauma, TEE showed a pericardial effusion (n = 1), a large trapped right atrial fat embolus (n = 1), and significant myocardial wall motion abnormalities consistent with myocardial contusion (n = 2), and excluded aortic dissection (n = 7). In unexplained postoperative hypotension or cardiac failure, TEE showed severe global impairment of left ventricular function (n = 1), a pericardial effusion (n = 2), major regional wall motion abnormalities consistent with myocardial ischaemia or infarction (n = 3), patch dehiscence (n = 1), and no abnormality (n = 3). In suspected prosthetic valve dysfunction, TEE showed paraprosthetic leakage (n = 3) and obstructed mitral prosthesis (n = 1), and helped exclude infective endocarditis. Neither of the patients investigated for postoperative neurological deficit had evidence of intracardiac thrombus or patent foramen ovale. In suspected aortic pathology, TEE showed a new thoracic aortic dilatation (n = 1) and excluded aortic dissection (n = 2). Elective postoperative monitoring showed a new regional wall motion abnormality in one patient with severe hypotension and persistent regional wall motion abnormalities in two patients. It also assisted in the diagnosis of hypovolaemia or impaired left ventricular function and excluded other complications in patients with moderate hypotension (n = 4). Thus TEE gave important diagnostic information in 24/27 patients studied acutely and 7/23 patients monitored electively.

TEE is a valuable diagnostic procedure in the cardiac surgical intensive care unit and may be of assistance in routine monitoring after coronary artery bypass surgery.

AIDS-associated heart disease relates to opportunistic infection rather than to the HIV virus: a study of 113 consecutive patients

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One hundred and thirteen consecutive homosexual men mean age 37 (range 23–57) with HIV infection were prospectively studied by Doppler echocardiography. Ninety five patients had the AIDS syndrome (group A) for 19 (12) months and 18 patients had HIV infection without opportunistic infections (group B) for 43 (28) months. Doppler echocardiography was normal in 38 patients (40%) of group A and in 14 patients (78%) of group B. Pericardial effusion was found in 40 patients (43%) of group A and in only two patients of group B. Left ventricular dilatation, or dysfunction, or both was found in 17 patients (18%), aortic root dilatation and aortic regurgitation in seven patients, and an intracardiac echogenic mass in six patients (6%) of group A, but were not documented in group B. Mitral valve prolapse, or mitral regurgitation, or both was found in 26 and two patients, isolated right ventricular dysfunction and dilatation in three and one patients of group A and group B respectively. Pneumocystis carinii occurred in 57 (60%); cytomegalovirus in 32 (34%); mycobacterium in 21 (22%); toxoplasmosis in eight (8%); and Kaposi sarcoma in 36 (38%) patients. Forty one patients in group A had a cardiac presentation; of these nine had cardiomegaly with clinical signs of heart failure and a further nine patients had tachyarrhythmias compared with only one patient with such presentation in group B. Despite the CD4 lymphocyte count (%) being significantly lower in group A than in group B (5·1 (5·4) *v* 15·5 (5·8), $p < 0{\cdot}0001$, (normal 27 to 49)), statistical analysis showed that the CD4 count is not correlated to the presence of pericardial effusion, left ventricular dysfunction, right sided cardiac enlargement, or the duration of HIV infection in both groups.

Although often not diagnosed clinically, cardiac involvement in patients with AIDS is a clinical reality. Pericardial effusion, cardiomyopathy, and left ventricular dysfunction appear to have a high prevalence in male homosexual patients with AIDS. These echocardiographic abnormalities are associated with clinically apparent intercurrent infections, which appear to be the culprit for cardiac involvement, rather than the HIV virus or the severity of infection as reflected by the CD4 count. These findings have important implications for future therapeutic studies in patients with AIDS related heart disease.

Is HIV cardiomyopathy caused by selenium deficiency?

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Cardiomyopathy due to selenium deficiency is endemic in the Keshan district of China. It may also occur in the context of human immunodeficiency virus (HIV) infection. To test this hypothesis, we have measured serum selenium concentrations in nine HIV positive patients with cardiomyopathy and nine HIV positive controls with echocardiographically normal hearts matched for age, sex, risk group, body mass index, and CD4 count (a measure of the severity of HIV disease). Cardiomyopathy was defined as global hypokinesia of the left ventricle and fractional shortening of less than 28%. Selenium assay was performed using carbon atomic absorption spectroscopy. The normal ranges for serum selenium concentrations and CD4 count in our laboratory are 0·86 to 1·6 μmol/l and 800 to 1500 cells/mm^3 respectively. The patients with HIV cardiomyopathy had a mean CD4 count of 25·8 (50·3) cells/mm^3, serum selenium concentration 0·36 (0·19) μmol/l, and body mass index of 19·31 (3·53) kg/m^2. Those with normal hearts had a mean CD4 count of 40·4 (40·1) cells/mm^3, serum selenium concentration 0·59 (0·27) μmol/l, and body mass index of 19·00 (2·87) kg/m^2. Only the selenium values were significantly different between the two groups ($p < 0·05$).

Selenium deficiency is common in late stage HIV infection. Patients with HIV cardiomyopathy have a significantly lower serum selenium concentration than HIV positive patients matched for stage of disease and body mass index. This suggests that selenium deficiency may play a part in the pathogenesis of HIV related cardiomyopathy.

Symmetrical and asymmetrical ^{123}I-metaiodobenzylguanidine scans in patients with long QT syndromes

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The arrhythmogenic mechanism in congenital long QT syndromes has been proposed to be an imbalance of the cardiac sympathetic innervation. I^{123} metaiodobenzyl-guanidine (MIBG) is an analogue of noradrenaline which is taken up by the sympathetic nerve terminals and can be used for visualisation of the cardiac sympathetic nerve supply. This study examines the regional sympathetic innervation in patients with long QT syndromes and compares this with the result in normal control patients. Four patients with long QT syndromes (age range 19–55; all women QTc $>0·44$ s in all) were studied and compared with a control group consisting of six patients with atrioventricular reentrant tachycardia and eight patients with normal coronary arteries at angiogram and no evidence of fixed or reversible ischaemia on thallium-201 scanning. Patients attended fasting, and were given 370 mbq per 1·73 m^2 of body surface I^{123} MIBG via a peripheral vein. SPECT gamma scanning was performed three hours later by a single pass with 45 s per step (64 × 64 matrix). Left ventricular MIBG uptake was processed into bull's eye target plots. The inferior portion of the scan frequently exhibited artifacts due to uptake of MIBG in the liver or spleen and was not used for statistical analysis. Asymmetry of MIBG uptake was defined as the ratio of uptake in the upper quadrants (posterior:anterior) beyond the range 0·95–1·25 (derived from mean (2 SD) from the control group). None of the patients in the control group had an abnormal ratio. Of the patients with long QT syndromes, two had abnormal scans (ratios 1·31 and 1·29) suggesting decreased sympathetic supply on the septal surface of the left ventricle, the other two patients had symmetrical scans (ratios 1·1 and 1·1). The left cervical ganglion supplies the superior and posterior portion of the ventricle and the right cervical ganglion the anterior and septal portion.

The results of this study suggest that some patients with long QT syndromes have relative denervation in the area supplied by the right cervical ganglion, but there are patients who have completely normal scans. This suggests that asymmetry of cardiac sympathetic nerve supply may not be the sole mechanism leading to the genesis of long QT syndromes.

Evidence of asymmetrical cardiac sympathetic innervation in the Romano-Ward syndrome from studies using ^{123}I-metaiodobenzylguanidine

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The Romano-Ward syndrome is a congenital cause of a prolonged QT/U interval and is thought to be due to an imbalance between the left and right sympathetic innervation of the heart. ^{123}I-metaiodobenzylguanidine (MIBG) is an analogue of noradrenaline and is taken up into the postsynaptic nerve terminals. The distribution of the sympathetic supply to the heart can thus be assessed by single photon emission computed tomography (SPECT). Eight patients with proven normal coronary arteries and left ventricular contraction, as assessed by cardiac catheterisation, were compared with a family of three patients (mother and two daughters) with Romano-Ward syndrome. Only one of these patients was symptomatic with periodic polymorphic ventricular tachycardia, the others not exhibiting any significant dysrhythmias on either stress or ambulatory electrocardiographic monitoring. Three hour MIBG uptake was assessed both subjectively and objectively using a radial, segmental method of SPECT analysis. Both asymptomatic members of the family had a distribution of isotope comparable with the controls. The symptomatic family member had a significantly asymmetric distribution, with more activity present within the lateral wall.

This finding supports an asymmetric sympathetic innervation of the heart in patients with symptomatic Romano-Ward syndrome.

Transcatheter occlusion of patent arterial ducts: six years' experience at Guy's Hospital

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Since 1986, of 147 patients in whom transcatheter occlusion of a patent arterial duct with an umbrella device was attempted, a first device was successfully implanted in 134 (91%) patients. In the remaining 13, the duct had unusual anatomy in two, was too small in six (two previously surgically ligated), and was too large in three. Abnormal systemic venous anatomy precluded passage of the introducer sheath in two. The age at implantation ranged from seven months to 67 years (median 2·87 years) and weight from 6·15 to 79·6 Kg (median 13·7 Kg). Two patients had had a previous Senning operation and five had had previous duct ligation. A 12 mm device was implanted in 93 patients and a 17 mm device in 41. A complete arteriovenous guidewire circuit was established to position the introducer sheath in seven patients. Complications of the procedure included embolisation of the device to the femoral artery in one patient and severe haemolysis needing surgical removal of the device in one patient. No case of infective endarteritis occurred. At the latest follow up colour Doppler study confirmed complete occlusion of the duct in 92 (69%) patients after implantation of a single device. Of the 42 patients with residual leak 22 have follow up of less than four months. Of those patients with follow up of more than four months, 17 subsequently had attempted implantation of a second device, which was successful in 16 (94%). The duct in the remaining patient could not be dilated sufficiently to allow passage of the delivery system. After a mean follow up of eight months, 13 ducts are completely occluded on colour Doppler study. Three ducts still have a small residual lead one day, six weeks, and 18 months after the second insertion.

Transcatheter occlusion of a patent arterial duct is feasible and is associated with few complications. There is an important incidence of residual leak and implantation of a second umbrella device is sometimes needed to achieve complete occlusion.

Improved left ventricular subendocardial function after coronary angioplasty

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The subendocardial fibres in human myocardium are longitudinally arranged. To assess whether their resting function is impaired by coronary artery disease, we compared 22 patients before and after successful single vessel coronary angioplasty (13 left anterior descending, two circumflex, and seven right coronary artery), with 25 age matched normal subjects. Long axis function was measured with M mode echocardiography of the left (L) and septal (S) sites of mitral ring motion with simultaneous phonocardiography, together with transverse cavity dimension and wall thickness. M-mode records were digitised. Transmitral flow was assessed by pulsed Doppler. In 18/22 patients, basal long axis function was abnormal when compared with normals, with prolonged systolic shortening (L: 79 (26) ms *v* 52 (10), and S: 81 (29) ms *v* 50 (10), p values <0·05) beyond aortic closure, reduced early diastolic lengthening rates (L:4·8 (1·7) cm/s *v* 7·7 (1·9), and S:4 (1·7) cm/s *v* 6·7 (1·8), p values <0·05), and increased A wave amplitude (L:41·0 (7·0)% total excursion *v* 25·2 (6·5)%, and S:43·0 (7·1) *v* 27·5 (5·9)%). After angioplasty, the duration of aortic closure—maximum shortening—fell to 57·0 (21·0) ms (L) and 59·0 (23·0) ms (S) (p values <0·001), early diastolic velocities increased to 5·5 (1·8) cm/s (L) and 4·7 (1·8) cm/s (S) (p values <0·001), and A wave amplitude fell to 37·1 (8·2)% total excursion (L) (p < 0·01) and 42·0 (7·1)% (S) (p < 0·5), at both sites. At the same time, left ventricular posterior wall thinning rate increased to 6·0 (2·0) *v* 4·8 (1·7) cm/s (p < 0·001), and the Doppler E/A ratio rose from 0·9 (0·3) to 1·1 (0·3) (p < 0·001). There was no significant difference in the rates of minor axis change.

Thus in patients requring angioplasty diastolic subendocardial function is often abnormal even in the absence of angina. These changes are promptly reversible by angioplasty, strongly suggesting that they are the direct effect of coronary stenosis. The results show the interrelations between subendocardial function, left ventricular wall dynamics, and filling pattern.

Are transoesophageal ultrasound studies required to select patients for transcatheter closure of atrial septal defects?

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Transoesophageal echocardiography has been shown to be a prerequisite for successful transcatheter clamshell occlusion of atrial septal defects. Its value in patient selection, however, has as yet not been assessed. We studied 38 patients (age 3 to 66) with the clinical or precordial ultrasound (PE) diagnosis of atrial septal defect by transoesophageal ultrasound (TEE) techniques to define its relative value in patient selection. Precordial studies included subcostal and parasternal imaging and colour flow mapping; TEE was performed using single plane equipment in 17 patients and biplane equipment in 21. All studies were performed using a standard examination protocol. Cardiac catheterisation and angiography were carried out in 15 patients. All PE and TEE studies were analysed by two independent observers and patients were assigned to three categories: (*a*) those who were unsuitable for clamshell occlusion, (*b*) those who might be, and (*c*) those who were judged to have a perfect anatomy for device occlusion. On the basis of the TEE study 11 patients were judged to be unsuitable for transcatheter closure, of whom 10 subsequently underwent surgical defect closure. Only five of these were identified by PE. Important information missed by PE in this group included sinus venosus defect in two, posterior defect in one, and multiple large defects in two. Defects with multiple fenestrations were documented by TEE in a further four patients (only 2 by PE), in whom clamshell occlusion, however, appeared to be feasible. Deficiency of the anterosuperior margin of the defect (eight patients), which may preclude effective occlusion of the defect, was better documented by TEE than by PE. Optimal anatomy for device occlusion was suggested by 17 of the 31 patients in whom adequate quality images were obtained. This was confirmed by TEE in 13 and in another three patients in whom PE remained ambiguous.

Thus TEE imaging allows a comprehensive tomographic assessment of atrial septal defects and their relation to near by structures. In children PE allows for adequate patient selection in the majority of cases. In older children, adolescent, and adult patients TEE appears to be the technique of choice for patient selection; TEE should be performed in all patients in whom PE gives inadequate images or cannot show fully the entire defect margin and its relation to other structures.

Physical activity, hypertension, and risk of heart attack

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Physical activity is associated with a reduced risk of heart attack. Several studies have shown, however, that at vigorous levels of physical activity in middle aged men there may be an increase in the risk of heart attack above the level seen in moderate or moderately vigorous men. This phenomenon has been found in the British Regional Heart Study and the data have now been explored to determine possible mechanisms for this unexpected finding. The group comprises 7735 men aged 40 to 59 years drawn from one general practice in each of 24 towns. The men were classified into six broad categories based on their usual reported activity: inactive, occasional, light, moderate, moderately vigorous, and vigorous. All men were followed up for 9·5 years for cardiovascular morbidity and all cause mortality. Men without evidence of pre-existing ischaemic heart disease were separated into normotensive ($n = 3888$) and hypertensive ($n = 1806$) groups, ie systolic BP > 160 mm Hg or diastolic BP > 90 mm Hg or on regular antihypertensive treatment. In normotensive men there was an inverse relation between physical activity and heart attack. In hypertensive men there was a decline in risk to levels of moderate and moderately vigorous activity followed by an increase in risk in the vigorously active group. When other risk factors were taken into account, the increased risk of heart attack in vigorously active hypertensive men was more pronounced than before such adjustment. The phenomenon was most apparent in the younger (40 to 49 year old) men.

Analysis of interactions between risk factors suggests that hypertension was the critical factor in determining the increased risk of heart attack in vigorously active younger middle aged men. These findings are highly relevant to the current promotion of physical exercise in the management of hypertension.

Alcohol and sudden cardiac death

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Heavy drinking may induce cardiac arrhythmias and ventricular tachycardia, mechanisms associated with sudden cardiac death. The association, however, between heavy drinking and the risk of sudden cardiac death in the general population is uncertain and reported findings have been inconsistent. The relation between alcohol and sudden death from ischaemic heart disease has been examined in a large prospective study involving 7735 middle aged British men drawn from general practices in 24 towns (The British Regional Heart Study). During the follow up period of eight years there were 217 deaths from ischaemic heart disease of which 117 (54%) were classified as sudden (death occurring within one hour of the onset of symptoms). Although heavy drinkers (>6 drinks/day) did not show high incidence rates of death from heart attacks, they showed the highest rates of sudden cardiac death. Nondrinkers showed the lowest rates. Deaths which occurred in heavy drinkers were predominantly sudden (75%) and this was seen in all men, irrespective of the presence or degree of pre-existing ischaemic heart disease. The increased incidence of sudden death in heavy drinkers was most apparent in men without pre-existing evidence of ischaemic heart disease, with heavy drinkers showing a 60% increase in risk compared with occasional or light drinkers even after adjustment for age, social class, and smoking. In men free of ischaemic heart disease, heavy drinkers had marginally significantly higher incidence rates of sudden death than all other drinkers combined ($RR = 2{\cdot}00$, 95% CI 0·98–4·8, $p = 0{\cdot}06$) after adjustment for age, social class, and smoking. Further adjustment for systolic blood pressure reduced the risk to 1·7.

This study suggests that heavy drinking is associated with an increased risk of sudden death, possibly due to a direct effect of alcohol on the myocardium.

Bovine internal mammary artery grafts: do they remain patent?

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A successful outcome after coronary artery bypass surgery depends largely upon the choice of graft conduit. It is well established that the best long-term results are obtained with internal mammary artery grafts but autologous saphenous vein and the gastroepiploic artery are useful alternatives. Other conduits such as cephalic veins and synthetic grafts have proved grossly inferior. With increasing numbers of patients requiring reoperation plus a proportion of new patients presenting with insufficient or poor quality saphenous veins, there is a need to find a more suitable conduit that is readily available, easy to handle, and has good long-term patency. To this end, bovine internal mammary artery grafts have been developed. We have used a total of 26 such grafts in 18 patients since January 1990. There were 13 men and five women, men age 61 (range 52 to 71). Two patients died, one at 10 months, due to cardiac failure and the other at four months, after myocardial infarction. Postoperative angiography has been performed in 11 of the other 16 patients, at a mean of 10 months after surgery (range 3 to 23 months). Of 15 bovine internal mammary artery grafts implanted and restudied, three are currently patent (20%). We report the results of clotting studies and analysis of lipid state. These patients do not appear to represent an atypical group, either in terms of coagulopathy, native coronary artery size, or the type of vessel disease.

This is the largest experience and longest follow up of bovine internal mammary artery grafts so far reported. Our poor results, however, contrast with the early enthusiasm from other centres.

Impaired myocardial endothelial and non-endothelial dependent microvascular function in patients with coronary occlusive disease after cardiac transplantation

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Coronary occlusive disease is the major long-term problem after cardiac transplantation. It is a diffuse disease which also affects smaller coronary vessels and is difficult to assess angiographically. Coronary flow measurements allow investigation of vasodilatory responses in the coronary microvasculature. We investigated the hypothesis that coronary flow responses (CFR) to papaverine (a non-endothelial dependent vasodilator) and acetylcholine (an endothelial dependent vasodilator) are impaired in patients with coronary occlusive disease after cardiac transplantation. The CFR was assessed in 27 cardiac transplant patients with normal coronary anatomy (group 2) and 20 patients with evidence of mild coronary occlusive disease on angiography (mean % stenosis diameter 23 (SD 6)%) in a proximal coronary vessel (group 1), with 12 of these in the left anterior descending coronary artery (mean % stenosis diameter 24 (SD 8)%). A Doppler flow probe was inserted into the proximal left anterior descending coronary artery in each patient. Incremental doses of intracoronary papaverine (pap), and glyceryl trinitrate (GTN) followed by acetylcholine (Ach) were given until maximum hyperaemia was achieved. The CFR for each drug was defined as the ratio of resting (RFV) to peak coronary blood velocity. The CFR after papaverine was impaired in group 1 compared with group 2 patients, (2·5 (1·0) *v* 4·2 (1·0); $p < 0\cdot001$)). The CFR after Ach was impaired in group 1 patients compared with group 2, (1·8 (0·8) *v* 2·9 (0·9); $p = 0\cdot04$)). There was no difference in RFV after GTN (group 1 RFV 6·9 (5·0) before and 6·9 (6·0) cm/s after GTN; group 2 RFV 7·4 (4·7) before and 7·3 (5·5) cm/s after GTN), or in diameter of left anterior descending coronary artery between groups after the vasodilatory drugs.

Coronary endothelial and non-endothelial dependent microvascular responses are impaired in cardiac transplant patients with minor proximal coronary stenoses. This disturbance of cardiac microvascular function may contribute to the late morbidity and mortality seen in cardiac transplant patients with coronary occlusive disease.

Gated F18 fluorodeoxyglucose positron emission tomography: a novel approach for the detection of viable myocardium

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Detection of viable myocardium is important and should aid the decision making in coronary artery revascularisation and cardiac transplantation. A novel approach to detect regions of viable myocardium using gated fluorodeoxyglucose (FDG) positron emission tomography is described. This directly measures cardiac motion simultaneously with regional uptake of FDG. The alternative double isotope methods (FDG + perfusion imaging) increases the patient radiation dose and cannot take account of any alteration in myocardial characteristics occurring in the period between studies. Thirty six patients were studied consisting of 27 patients (mean age (SD) 58 (7·8); 22 men with chronic coronary artery disease and abnormal left ventricular contraction documented by cardiac catheterisation. Eight patients (mean age 55 (7·1); three men) with normal coronary arteries, left ventriculogram, and exercise electrocardiogram acted as controls. One patient had dilated cardiomyopathy. Patients were glucose loaded. Decay compensated scans were performed at six levels, 16 mm apart to cover the left ventricle. Data collection was gated into eight phases with the three dimensional matrix resliced into eight short axis sections for each phase. Radial shortenings were obtained at 32 angles for each short axis section. The left ventricular conformation was thus defined by 32 × 8 radial shortening distances. Conformational changes of radial shortenings and regional uptake of FDG were displayed using a bull's eye presentation. Cine loop images can also be viewed at any section or orientation. Viable myocardium was defined as a region of akinetic myocardium with good FDG uptake (FDG $\geqslant$ normal myocardial region). Viable myocardium was detected in three patients, one in the inferolateral, one in the anterior, and one in the anteroseptal region. Another study of a patient with dilated cardiomyopathy further validated the technique showing good global uptake of FDG but reduced contraction. Left ventricular angiography confirmed these regions of akinesis.

Gated FDG positron emission tomography can simultaneously detect regions of metabolically active myocardium with poor contraction using a single scan: these regions are potentially viable.

Post-infarct septal rupture in the elderly

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Age is often used as a discriminant when considering referral for cardiac surgery on both clinical and economic grounds. This is especially true for acute disorders, as elderly patients are said not to tolerate such surgery as well as younger patients. Rupture of the interventricular septum is a disastrous complication of acute myocardial infarction and carries a high mortality despite surgical intervention. We reviewed the experience of this hospital with elderly patients with this condition and of the referral pattern from peripheral hospitals. From 1980 to 1989, 108 patients with postinfarction septal rupture were seen. Twenty two patients were $\geqslant 70$ years of age and 86 were < 70. Site of infarction before rupture was anterior in 68% of those $\geqslant 70$ and 63% in those < 70. The spectrum of cardiac decompensation after rupture was similar in the two age groups although heart rate was lower (101 *v* 110/min, $p = 0\cdot037$) and systolic blood pressure higher (100 *v* 92 mm Hg, $p = 0\cdot1$) in patients $\geqslant 70$. Extent of coronary artery disease was similar (2 *v* 1·88 vessel disease). Intention to treat at our coronary care unit was for urgent repair in 6 (27%) $\geqslant 70$, (56 (65%) < 70); medical management before proposed repair in 12 (55%) $\geqslant 70$, (22 (26%) < 70); and four (18%) $\geqslant 70$, (eight (9%) < 70) were considered unsuitable for surgery ($p < 0\cdot01$). Thirteen (59%) $\geqslant 70$ had surgical repair of whom 10 (77%) survived; 68 (79%) < 70 had surgery of whom 33 (49%) survived. Of the admissions from the local population (79 000), 13/34 (38%) were $\geqslant 70$; only 9/74 (12%) patients referred from peripheral hospitals (population 809 000) were $\geqslant 70$ years of age ($p < 0\cdot01$).

Age alone should not deter referral for assessment as careful selection can produce an acceptable surgical mortality that compares favourably with that in a younger population in whom more elaborate surgery is often attempted. Referral rates from peripheral hospitals are low at all ages compared with the frequency of rupture found in the local population but referral of those ≥70 is disproportionately low.

Automatic recording of defibrillation on general medical wards by day and night: implications for ward design and staffing

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The outcome of ventricular fibrillation on general medical wards could depend upon the speed of defibrillation, particularly at night. Defibrillation was timed accurately on five of the six general medical wards. Each ward had a cardiac arrest call button, and the time of all calls was logged automatically by the hospital switchboard. Most patients were located in four-bed bays within 50 m of a defibrillator with a Tracker recorder to record automatically the time of switch on and first defibrillation, and all monitored rhythms. In 26 months, 67 recordings were obtained from 69 first episodes of ventricular fibrillation. Twenty eight patients were initially resuscitated, and 17 survived to be discharged. Major non-cardiac illness before ventricular fibrillation was associated with increased mortality (4/41 *v* 13/27, 1 set of data incomplete, p = 0·001). Ventricular fibrillation that occurred during the daytime nursing shift (07:30–15:30 hours) was associated with increased survival compared with ventricular fibrillation at other times (10/23 *v* 7/46, p = 0·01). No patient who developed ventricular fibrillation between 20:00 hours and 04:00 hours survived. Ventricular fibrillation was evenly distributed over the 24 hour period and, importantly, there was no significant diurnal variation in response intervals. Outcome was not related to the time from cardiac arrest call to monitor connection (median 125 s, range 0–620), or the time from call to defibrillation (median 181 s, range 37–662). Ventricular fibrillation was displayed for longer than 60 s before the first defibrillatory shock in 27 recordings, and four patients were given further shocks without clear indication.

This automatic recording system provides an effective audit of defibrillation. The poor results at night could be due to late detection of cardiac arrests, or less efficient initial resuscitation. Staffing levels were reduced at night, and night shift staff may have difficulty attending resuscitation training. Survival might be better on open plan wards.

Coronary vasomotor effects of serotonin in patients with angina: relation to coronary stenosis morphology

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Previous experimental studies have shown that the effect of serotonin (5-HT) on a coronary stenosis depends on whether that stenosis is compliant or fixed. The relation, however, between morphology of coronary stenosis and the response to 5-HT in patients with angina is not known. Using computerised quantitative coronary angiography we studied the effects of intracoronary infusion of 5-HT on 38 coronary stenoses of different morphology (concentric, eccentric, complicated) in 11 patients with stable angina and four with variant angina. In response to the maximum infused concentration of 5-HT, 100% of complicated stenoses and 50% of concentric stenoses constricted by >20% (p < 0·05). The magnitude of constriction was greater at eccentric stenoses (32·08 (4·1)%) than concentric stenoses (15·68 (2·8)%, p < 0·05), and greater at complicated stenoses (57·69 (7·6)%, p < 0·05) than eccentric stenoses. At complicated stenoses the constriction was greater (0·85 (0·16) mm, p < 0·05) than at the adjacent reference segments (0·42 (0·12) mm). It was similar to the reference segment for both concentric and eccentric stenoses. The constriction at the stenosis was greater for complicated lesions than for smooth (concentric and eccentric) lesions in both patients with stable (51·8 (7·3) *v* 22·5 (4·1)%, p < 0·001) and variant (77 (17) *v* 28·2 (8·1)%, p < 0·05) angina. There was a weak correlation (r = 0·38) of magnitude of constriction with length of stenosis, but not with severity of baseline stenosis.

In these patients the magnitude of the vasoconstrictor response to 5-HT at the site of an atheromatous coronary plaque depends on the morphological characteristics of the plaque and is more closely related to irregular contour than severity or length of stenosis. This relation suggests that variations in receptor type, or density, or in the smooth muscle cell response to stimulation may determine the response to locally released 5-HT in patients with coronary disease.

Invere relation between serum lipoprotein (a) concentrations and first phase insulin secretion

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Elevated serum lipoprotein (a) (Lp(a)) concentrations are often seen in patients at high risk of coronary heart disease. Recently, raised LP(a) concentrations have been reported in both insulin dependent and non-insulin dependent diabetes mellitus, conditions associated with increased risk of coronary heart disease. Consequently, it has been suggested that raised serum concentrations of Lp(a) contribute to the increased risk of coronary heart disease in these subjects. To investigate whether an association exists between serum Lp(a) concentrations and insulin metabolism, serum Lp(a) was measured in 146 healthy non-obese men in whom insulin metabolism had been assessed by an intravenous glucose tolerance test with measurement of plasma concentrations of glucose, insulin, and C-peptide. When subjects were stratified according to quartile of serum Lp(a) distribution, an inverse relation was seen with the first phase insulin response to glucose. This finding was supported by further analysis of these data using mathematical modelling, which showed an inverse relation between serum Lp(a) and both first phase insulin secretion and responsiveness. No association was seen between serum Lp(a) concentration and insulin resistance, implying that Lp(a) operates independently of the constellation of metabolic disturbances associated with coronary heart disease (Reaven's "Syndrome X"), which centre on the state of insulin resistance.

These findings suggest a role for Lp(a) in the development of chronic atherosclerotic complications in diabetic patients as well as increasing risk of coronary heart disease in healthy subjects.

Mechanisms of intracellular pH recovery after global ischaemia in the perfused heart

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The mechanisms of recovery of intracellular pH (pH$_i$) on reperfusion after ischaemia are not well understood. We have examined the relative roles of: (*a*) the Na^+-H^+ antiport; (*b*) HCO_3^- dependent acid extrusion; and (*c*) lactate efflux, on the recovery of pH$_i$ after total global ischaemia in the Langendorff perfused ferret heart. In hearts perfused with either HCO_3^- or nominally HCO_3^- free HEPES buffer the Na^+-H^+ antiport was inhibited by 1μM ethylisopropylamiloride ($K_i = 0{\cdot}15\mu M$). Total global ischaemia was produced by clamping the inflow line for 10 min. pH$_i$ was estimated using ^{31}P-nuclear magnetic resonance spectroscopy and effluent was collected for 2·5 min after reperfusion for lactate assay. Results are expressed as mean (SD). In HCO_3^--solution pH$_i$ fell from 7·08 (0·02) ($n = 5$) to 6·83 (0·02) after 10 min ischaemia. On reperfusion pH$_i$ recovered at 0·180 (0·05) pH units/min. In HEPES pH$_i$ fell from 7·05 (0·03) ($n = 5$) to 6·78 (0·02) after 10 min ischaemia and recovered at 0·116 (0·02) pH units/min on reperfusion ($p < 0{\cdot}05$ *v* HCO_3^-). In HEPES with the Na^+-H^+ antiport blocked pH$_i$ fell from 7·00 (0·04) ($n = 4$) to 6·77 (0·03) after 10 min ischaemia and recovered at 0·073 (0·04) pH units/min on reperfusion ($p < 0{\cdot}05$ *v* HCO_3; NS *v* HEPES). After 10 min ischaemia 6 (1·5) μmol lactate/g wet weight ($n = 15$) effluxed from the heart in the first 2·5 min of reperfusion. Proton coupled lactate efflux under the conditions of these experiments can account for 50% of pH$_i$ recovery in HCO_3^- perfused hearts, 80% in nominally HCO_3^- free buffer, and 100% in the nominal absence of HCO_3^- with the Na^+-H^+ antiport blocked (assuming an intracellular proton buffering capacity of approximately 25 μmol/g wet weight).

The Na^+-H^+ antiport is not the major mediator of the recovery of pH$_i$ after global ischaemia in the perfused ferret heart. Recovery of pH$_i$ is principally a result of activity of an eternal HCO_3^- dependent mechanism and a second process consistent with proton coupled lactate efflux.

Closure of arteriovenous fistulas in renal transplant recipients: long-term haemodynamic benefits

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The longer-term haemodynamic consequences of planned surgical closure of arteriovenous fistulas in patients after successful renal transplantation have not been described. This study measured exercise performance on treadmill, echocardiographic estimation of chamber dimensions and Doppler cardiac output in a group of 11 patients (mean age 41) with normal renal function at a mean of 21 months after renal transplantation. They were studied before closure and at a mean of five months after closure. Five of these patients were reinvestigated at a mean of 15 months after closure. Exercise duration increased by 10% by five months with respect to initial values (621 (206) to 684 (192), $p = 0{\cdot}004$). Systolic blood pressure and rate pressure product at peak exercise were not significantly different. Resting systolic blood pressure was unchanged. In those patients followed up for 15 months, there was a further 4% increase in exercise times (455 (161) to 537 (163) s, $p = 0{\cdot}021$, to 560 (150) s, $p = 0{\cdot}017$). There was no significant change in peak blood pressure or maximal rate-pressure product. Stroke distance fell by 13% by five months (28·2 (5·1) to 24·6 (4·8) cm, $p = 0{\cdot}004$) and remained lower at 15 months. Cardiac output fell by 10% at five months and remained lower at 15 months (6·1 (1·6) to 5·5 (1·5) to 4·8 (0·3) l/min, $p = 0{\cdot}024$). Left ventricular end systolic and end diastolic dimensions were not significantly altered at either follow up time, but there was a trend to lesser left ventricular hypertrophy. Posterior wall thickness fell from 14·6 (1·9) to 12·9 (1·1) cm, and septal thickness reduced from 17·4 (2·8) to 15·0 (1·8) cm, $p = 0{\cdot}039$. Medication was constant during the study and patients noticed a subjective improvement.

This study shows that short-term haemodynamic improvements are continued to the longer-term after elective surgical closure of arteriovenous fistulas in patients with normal renal function after renal transplantation. Patients have a lower resting cardiac output than before closure and are able to exercise for longer at the same work expenditure. These findings strengthen the case for routine closures of fistula after successful renal transplantation.

Prolonged QT interval in type 1 diabetes: information from idential twins

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Type 1 diabetic people suffer sudden death from cardiorespiratory arrest. To determine whether QT interval prolongation may provide a substrate for this sudden death and whether this is related to autonomic neuropathy, we assessed QT interval in 34 monozygotic twin pairs discordant for type 1 diabetes and compared with 34 normal control subjects of similar age and sex. The twins (16 male) were aged from 10 to 42 years and the diabetic twins had a mean disease duration of 15 years. All subjects were normotensive, had no clinical cardiac ischaemia, and were taking no medications except for insulin in the diabetic twins. Autonomic neuropathy was assessed as (*a*) the fall in systolic blood pressure after one min of standing (>20 mm Hg = abnormal); and (*b*) the changes in heart rate during deep breathing, during Valsalva manoeuvre, and on standing. These tests were assessed by computer and graded by a conventional protocol. Resting heart rate, corrected QT interval, and the frequency of autonomic neuropathy were all significantly higher in diabetic twins than their non-diabetic co-twins (81 (13) *v* 72 (15) beats/min, $p < 0{\cdot}0005$; 429 (18) *v* 408 (13) ms, $p < 0{\cdot}005$; and 24% *v* 3%, $p < 0{\cdot}02$ respectively) but there were no differences between the non-diabetic twins and normal control subjects. Twins with diabetes > 15 years ($n = 17$) had a significantly longer corrected QT interval than their non-diabetic co-twins (423 (18) *v* 408 (12) ms, $p < 0{\cdot}005$); by contrast, this difference was not detected in twins with shorter duration of disease. Diabetic twins with autonomic neuropathy had a similar corrected QT interval (n = 8) when compared with diabetic twins without autonomic neuropathy (n = 26). Prolongation (>440 ms) of corrected QT interval was present in 4/34 (12%) diabetic twins, two of whom did not have autonomic neuropathy. In long standing type 1 diabetes, corrected QT interval may be prolonged, is not related to autonomic neuropathy, and may provide the substrate for sudden death.

A novel monoclonal conjugate with powerful antiplatelet and fibrinolytic properties which localises to damaged endothelium

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We have developed a molecular conjugate (R2) comprising an anti-platelet glycoprotein, a IIb/IIIa (M735) monoclonal antibody (MAb), an antidamaged endothelial cell MAb (P14G11), and urokinase (Ur) using succinimidyl 3-(2-pyridyldithio) propionate (SPDP) as a coupling reagent. Specific Ur activity of R2 was 10 000 IU/mg protein. Fibrinolytic activity of the conjugate was confirmed with fibrin plates and a chromogenic substrate assay for Ur. Whole platelet preparations confirmed targeting of R2 for platelets. Localisation of R2 to damaged endothelial cells was shown using scratch damaged endothelial monolayers and peroxidase coupled second antibody technique. Inhibition of platelet aggregation was assessed with 20 μM adenosine diphosphate and 4 μg/ml collagen as agonists and five μg of R2 completely inhibited platelet aggregation (Ag) induced by either of these reagents. By contrast 12 μg of M735 alone was required to inhibit platelet aggregation by collagen and this dose only decreased platelet aggregation with adenosine diphosphate to 66% of control. The effect of R2 on coagulation was shown to be at least equivalent to Ur and M735 alone (whole blood clotting ratio for R2 = 1·26, Ur = 1·13, M735 = 1·18).

A conjugate with enhanced anti-platelet and thrombolytic properties has been developed that localises to sites of damaged endothelium such as occur after coronary angioplasty. Such molecules will be tested for their effects on acute closure and medium term restenosis.

Real time, echocardiographic analysis of ventricular function by automatic boundary detection

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Left and right ventricular function may be studied in real time by new methods of echo signal processing based upon tissue characterisation. Identification and separation of blood and myocardial tissue structures is performed automatically down each image scan line. From this, the blood tissue interface is recognised over the entire image and used to create an endocardial boundary. An operator defined region of interest may be drawn over the left or right ventricles and the ventricular area is continuously calculated for each image frame. A real time graphic display of ventricular area is displayed together with the fractional area change (FAC), an ejection fraction analogue, which is updated for each cardiac cycle. Assessment of ventricular contractility or filling rates is obtained by real time analysis of rate of area change (dA/dT). This system has been currently evaluated in 20 unselected patients undergoing routine echocardiographic study. A total of 160 parasternal short axis or apical four chamber imaging planes were evaluated for ventricular function analysis. Two operators scanned each patient to allow analysis of inter and intraobserver variability. 51 (31%) image studies were rejected because successful tracking of at least 75% of the endocardial boundary could not be obtained. In those studies where good endocardial tracking was obtained, inter and intraobserver variability respectively for ventricular area (15%, 12%), FAC (16%, 11%), and dA/dT (13%, 11%) were obtained. The average study time was 4·25 (1·1) minutes.

Thus this new system provides rapid real time, non-invasive assessment of ventricular function and it may be used successfully in most patients with acceptable variability. It is clearly of potential value in the study of the effect of therapeutic interventions and therefore warrants further validation and clinical assessment in this context.

High apolipoprotein(a) concentrations are associated with increased cardiac risk in patients undergoing peripheral vascular surgery

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Apolipoprotein(a) (apo(a)) concentrations are genetically determined and are associated with the presence of coronary artery disease in patients with peripheral vascular disease. The close structural homology that exists between apo(a) and plasminogen has implied an important link between lipoprotein metabolism and the clotting/fibrinolytic system. We have investigated the role of apo(a) analysis in the preoperative cardiac risk assessment of 39 consecutive patients undergoing peripheral vascular surgery. Apo(a) concentration was measured in fasting serum by an immunoradiometric assay with monoclonal antibodies to two different epitopes of apo(a). Coronary arteriography and dipyridamole thallium scintigraphy were also performed in all subjects. Perioperative cardiac complications occurred in six patients (15%; one of which was fatal). Of these six patients, five had apo(a) concentrations that were greater than the cohort median (197 U/l; sensitivity *v* specificity 83% *v* 52%), five had appreciable coronary artery disease (⩾one vessel ⩾50% diameter stenosis; 83% *v* 36%), and four had one or more reversible thallium defects (67% *v* 13%). Patients with apo(a) concentrations >197 U/l had a 5·3-fold increase in the prevalence of cardiac complications. All three tests were abnormal in the patient who died.

These results indicate that high concentrations of apo(a) are associated with an increased incidence of perioperative cardiac complications in patients undergoing peripheral vascular surgery. The measurement of apo(a) concentrations may prove to be a simple and reliable means of identifying those at greatest risk and may emerge as a useful additional tool in the preoperative assessment of this group of patients.

Ventricular interactions in pulmonary hypertension: impaired left ventricular filling caused by prolonged right ventricular systole

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To examine the effects of pulmonary hypertension (PH) upon left ventricular diastolic events, we studied 29 patients with PH and 10 controls with an enlarged right ventricle but normal pulmonary artery pressure, with echocardiography and Doppler and phonocardiography. Septal thickness, cavity dimensions, right ventricular-atrial (RV-RA) gradient, isovolumic relaxation time, and left ventricular filling patterns were measured. The peak RV-RA gradient was 60 (16) mm Hg in PH patients, and 18 (5) mm Hg in controls. The time intervals of pulmonary closure to the end of the tricuspid regurgitation and to the onset of tricuspid flow were both prolonged in patients with PH compared with controls (115 (60) ms and 120 (40) *v* 40 (15) and 45 (10) (mean (SD)), p values $<0·001$). On transmitral Doppler, 23 of 29 patients with pH had a dominant A wave; all controls had a dominant E wave. Left ventricular isovolumic relaxation time was prolonged in PH compared with controls, both as aortic closure to mitral valve opening (80 (25) ms *v* 50 (15)), and to the onset of mitral flow (105 (30) ms *v* 60 (15), p values $<0·001$). The delay from mitral opening to the onset of transmitral flow was longer in PH patients compared with controls (30 (15) ms *v* 10 (10), $p < 0·001$). At the time of mitral opening, there was a RV-RA gradient of 12 (10) mm Hg in PH, and on M-mode, 20/29 patients had evidence of posterior septal displacement during isovolumic relaxation. The RV-RA gradient was negligible in controls (0·4 (0·3), $p < 0·001$), and none had septal displacement (0/10 *v* 20/29, $p < 0·0001$).

Prolonged right ventricular tension decline, the direct result of severe PH, causes prolonged tricuspid regurgitation. It persists until after mitral opening on the left side of the heart, where events during isovolumic relaxation are disorganised, and subsequent filling impaired. These effects are likely to be mediated through the interventricular septum; this right and left ventricular asynchrony may represent an unrecognised mode of ventricular interaction.

Balloon dilatation of valves in infants and children with carbon dioxide as the contrast agent

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We used carbon dioxide gas (CO$_2$) as the contrast agent for balloon dilatation of valves in 47 infants and children (25 male, 22 female). In addition to the peak systolic withdrawal gradient at catheterisation, the peak instantaneous gradient was also derived using continuous wave Doppler ultrasound 24 hours before, and 24 hours after the procedure. Balloon dilatation of the aortic valve was performed in 20 patients (including four neonates and four patients who had previously undergone surgical valvotomy) at a median age of 43 months (range 0·07–264) with a balloon to annulus ratio (mean (SEM) of 1·15 (0·05)). The peak systolic withdrawal gradient fell from 59 (5) to 22 (3) mm Hg ($p < 0·01$). New or increased aortic regurgitation occurred in 13 patients, but was $<$grade 3 angiographically in all but two cases. The peak instantaneous gradient fell from 78 (5) to 34 (3) mm Hg ($p < 0·01$), and has remained virtually unchanged (40 (6) mm Hg) over a follow up period of 5 (1) months. In 14 patients with pulmonary stenosis (median age 18 months; range 5–129) and with a balloon to annulus ratio of 1·46 (0·07) balloon dilatation reduced the peak systolic withdrawal gradient from 54 (9) to 20 (4) mm Hg ($p < 0·01$), and the peak instantaneous gradient from 67 (7) to 27 (5) mm Hg ($p < 0·01$). In one patient with predominant infundibular stenosis there was no change in the gradient. At follow up (mean 5 (1) months) the mean peak instantaneous gradient was 23 (6) mm Hg. In 11 patients with tetralogy of Fallot (median age 3 months; mean balloon to annulus ratio 1·8 (0·03)) balloon dilatation of the pulmonary valve produced an immediate increase in systemic arterial oxygen saturation from 75% (16) to 87% (12) ($p < 0·01$). Over a follow up period of 6·6 (1·2) months two patients have required further palliation with an aortopulmonary shunt.

CO$_2$ allows for rapid balloon inflation and deflation at low inflation pressures, with minimal disturbance of systemic blood pressure and cardiac rhythm. The greatly reduced inflation and deflation times enable the use of larger diameter balloons on smaller shafts, with less vascular trauma.

Effect of intravenous magnesium on tachycardia and cardiac arrest in acute myocardial infarction

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The use of intravenous magnesium in acute myocardial infarction is currently undergoing investigation in those treated with thrombolysis. The trials predating thrombolysis, however, are important as they allow the effect of magnesium alone to be quantified, against which its effect with thrombolysis can be judged, and they also provide the only information available on the effects of magnesium in those in whom there is a contraindication to thrombolysis. Nine randomised controlled trials concerning 984 patients with acute myocardial infarction were analysed. Eight of these were double blind and one was single blind. Intravenous magnesium administration was associated with a 49% reduction in ventricular fibrillation and tachycardia ($p = 0·0004$, 95% CI 24–66%). Five trials (467 patients) also noted the incidence of other forms of cardiac arrest and supraventricular tachycardia. There was a 72% (8 to 93%) reduction in the incidence of electromechanical dissociation ($p = 0·02$, and a 60% (−86% to 11%) reduction in the incidence of asystole ($p = 0·04$). The incidence of supraventricular tachycardias was reduced by 49% (0·3 to 0·89) ($p = 0·009$), in the group treated with magnesium.

In the subset of patients not receiving thrombolysis for acute myocardial infarction intravenous magnesium would be expected to substantially reduce the incidence of tachyarrhythmias and cardiac arrest.

Rapid exclusion of acute myocardial infarction in patients without SR elevation by serial enzyme analysis with novel analysers: myoglobin, creatine kinase, and creatine kinase-MB enzymes

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Early exclusion of acute myocardial infarction within six hours of onset in patients without ST elevation is desirable and should have important impact on the management of coronary care units, accident and emergency units, and the appropriate use of thrombolysis. This study set out to determine: (*a*) If myoglobin, creatine kinase, and creatine kinase-MB can be used for the early diagnosis of myocardial infarction (within six hours) in patients without ST elevation. (*b*) The optimal timing of blood collection for enzyme analysis. (*c*) If rapid analysers are accurate enough to provide the diagnosis. Fifty nine consecutive patients with suspected myocardial infarction were recruited in a prospective study. They consisted of 13 patients with myocardial infarction (seven without ST elevation) and 48 patients in whom infarction was subsequently excluded. Enzyme assays were performed by novel quantitative rapid analysers (result within 10 minutes) situated in the coronary care unit. Optimal timing for blood collection was determined by hourly sampling for six hours. A myoglobin threshold of 120 μg/l at four hours after the onset of chest pain gave a sensitivity of 88·56% for diagnosing myocardial infarction in patients without ST elevation, a specificity of 99·80%, and predictive accuracy of 96·80%. At six hours this was 97·92%, 99·73%, and 98·65% respectively. No patient with myoglobin < 120 μg/l at four hours was found subsequently to have infarcted. For creatine kinase-MB a threshold of 20 U/l at six hours gave corresponding figures of 81·55%, 92·25%, and 93·18%.

Myocardial infarction can be excluded within four hours by myoglobin analysis or six hours by creatine kinase-MB analysis. This permits patients at low risk of events to be moved early from the coronary care unit freeing beds for other patients.

Recovery of coronary resistive vessel function after successful coronary angioplasty

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Eleven male patients (mean age 54, range 44–67) with single vessel, left anterior descending (LAD) coronary artery disease, positive exercise electrocardiograms, and normal left ventricular function were studied before and after successful percutaneous transluminal coronary angioplasty (PTCA). The coronary vasodilator response (CVR = maximal/basal myocardial blood flow (MBF) to intravenous dipyridamole (0·5 mg/kg over four min) was determined from Doppler measurement of coronary flow velocity and quantitative angiography. There was no significant change in CVR immediately after PTCA (mean (SD) 1·62 (0·44) before PTCA *v* 1·66 (0·60) after PTCA). In nine patients (eight with negative exercise electrocardiograms at seven days), basal and maximal regional MBF, and CVR, were determined at one, seven and 100 days after PTCA using dynamic 15 slice positron emission tomography with $H_2{}^{15}O$. Regional MBF measurements from myocardial regions subtended by the LAD (PTCA region) were compared with those from a myocardial region subtended by an angiographically normal artery (remote region). At one, seven, and 100 days after PTCA in eight patients without restenosis, basal MBF was 1·25 (0·26), 1·11 (0·16), and 1·07 (0·07) ml/min/g respectively in the PTCA region, and 0·93 (0·16) (p < 0·01), 0·87 (0·15) (p < 0·05), and 0·96 (0·11) ml/min/g in the remote region. At one, seven, and 100 days after PTCA, MBF after dipyridamole was 2·13 (0·64), 1·97 (0·61), and 2·29 (1·00) ml/min/g in the PTCA region, and 2·73 (0·90) (p < 0·05), 2·46 (1·07), and 2·32 (0·57) ml/min/g in the remote region, respectively. Thus the calculated CVR was 1·76 (0·60), 1·76 (0·48), and 2·15 (0·97) in the PTCA region and 2·99 (1·03) (p < 0·01), 2·82 (1·07) (p < 0·05), and 2·42 (0·56) in the remote region at one, seven and 100 days respectively.

Hence, in these patients, the CVR in the PTCA region is impaired immediately after successful PTCA and this impairment persists for up to one week. This impaired CVR within the first 24 hours is due both to an increase in basal MBF and a decrease in maximal resistive vessel dilatation, and at seven days it is due to a persistent increase in basal MBF. By 100 days, in the absence of restenosis, resistive vessel function has returned to normal.

Independent value of heart rate variability for predicting sudden death after myocardial infarction

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The independent prognostic value of reduced heart rate variability for sudden death after myocardial infarction is still controversial. Therefore, predischarge clinical assessments and left ventricular angiography were carried out in 411 survivors of a first myocardial infarction who were followed up for between one month and five years. Heart rate variability was derived from predischarge Holter recordings as the baseline width of the frequency histograms of normal to normal RR intervals. Of the 411 patients, 226 (55%) received thrombolytic therapy and 173 (42%) were discharged on β blockers. There were 103 (25%) patients with left ventricular ejection fractions < 40%: 82 (20%) of the patients were treated for heart failure in hospital. The predictive value of reduced heart rate variability (< 150 ms) for sudden death was examined using proportional hazards analysis. There were 13 (3%) sudden deaths. The estimated probability of sudden death in the first year was 4% without heart rate variability in the model. Given heart rate variability, the estimated probability of sudden death in the first year was 9% if heart rate variability was < 150 ms, but only 1% if > 150 ms (relative risk 8·3; 95% CI: 2·2–30·7; proportional hazards regression coefficient −2·12).

Reduced heart rate variability provides independent prognostic information in survivors of acute myocardial infarction.

Giving up smoking: how rapidly does risk of heart attack disappear?

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There is disagreement about the time required for the smoking associated risk of ischaemic heart disease to disappear after stopping smoking. The 9·5 year data from the British Regional Heart Study, a prospective study of cardiovascular disease among 7735 men age 40 to 59 years randomly drawn from one general practice group in each of 24 British towns, were examined to determine how rapidly the excess risk of ischaemic heart disease disappears after stopping smoking. The risk of ischaemic heart disease relative to never smokers was 2·1 (95% CI 0·8–1·6) in current cigarette smokers and ex-smokers respectively, after excluding men with a doctor's diagnosis of angina or previous heart attack and adjusting for age, systolic blood pressure, and serum total cholesterol concentration. Primary pipe or cigar smokers appear to carry no excess risk (relative risk = 1·1 (0·5–2·4) whereas secondary pipe or cigar smokers showed a relative risk of 1·8 (2·7–1·2) which is nearly as high as in current cigarette smokers. Separating ex-smokers according to the number of years since stopping smoking before the initial screening, we found a significant trend of declining risk with increasing years since smoking. Thus, ex-smokers had some benefit in the first two and 3 to 5 years since smoking and most of the excess risk disappeared in 6 to 10 years. In light ex-smokers (<20 cigarettes/day) no excess risk was seen after five years since smoking, but in heavy ex-smokers ($\geqslant 20$ cigarettes a day) the increased risk continued for up to 10 to 20 years after stopping. The benefit of stopping smoking was found to be more gradual than usually thought to be the case and switching from cigarettes to pipe or cigars does not appear to reduce the risk.

Although the benefit from stopping smoking should be stressed, emphasis should be put on educating the young not to start smoking and on advising current smokers to stop smoking altogether as early as possible.

Altered coronary flow reserve and metabolism in myocardium subtended by normal arteries in patients with coronary artery disease

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Myocardial blood flow (MBF) in regions subtended by angiographically normal arteries (ANA) was assessed in 13 patients (mean age 60, 10 men) with single vessel disease by dynamic positron emission tomography with ^{15}O-labelled water at rest and after intravenous dipyridamole (0·56 mg/kg over four min). Seven patients had left anterior descending disease (LAD) and six had right coronary artery or left circumflex disease (RCA/LCX). The coronary vasodilator reserve (CVR; dipyridamole MBF: resting MBF) in regions subtended by a stenosis was 1·87 (0·86), and in regions subtended by ANA it was (2·90 (1·39)). Both values were lower than the average CVR (3·92 (0·89), $p < 0·05$ for both comparisons) measured in 12 control men (mean age 30). Another group of 10 patients (mean age 60; nine men), five with LAD disease and five with RCA disease, and a control group of six patients (mean age 47; four men) underwent simultaneous arterial and great cardiac vein blood sampling during maximal atrial pacing to measure glucose extraction, alanine extraction, lactate extraction, and myocardial oxygen extraction in regions subtended by a diseased artery (LAD) or by an ANA, that is, the LAD in patients with RCA disease. Oxygen extraction was the same in the diseased region (69 (3%)), the ANA region (67 (6)), and in controls (64 (7)). There was a decrease in lactate extraction in the LAD region (−18 (27)%), $p < 0·05$ compared with the ANA region (38 (17)%), or controls (26 (11)%). Glucose and alanine extraction were increased in both the diseased region, (8 (6)% and 6 (6)%) respectively, and the ANA region (6 (3)% and 4 (3)%), compared with controls (2 (3)% and −1 (3)%) ($p < 0·05$ *v* both diseased and ANA regions).

Thus CVR is reduced in regions subtended by ANA in patients with coronary artery disease elsewhere compared with control subjects; in addition, regions subtended by ANA are characterised by different glucose and alanine handling during pacing, although they do not show metabolic signs of ischaemia.

Radiofrequency catheter ablation for atrioventricular accessory pathways

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Radiofrequency catheter ablation is an emerging treatment for arrhythmias due to atrioventricular accessory pathways (APs) such as those seen in the Wolff-Parkinson-White (WPW) syndrome. Forty seven patients, with 52 APs, had AP ablation performed over a one year period, and were followed up for one to 13 (mean six) months. Electrophysiological study was performed before ablation in 34 cases (two at other institutions); 13 had combined electrophysiological studies and ablation. Patients were aged 16 to 56 (mean 30), and 28 were men. Symptom duration was 0·2 to 40 (mean 11) years, and eight had suffered syncope. Patients had taken nought to six (mean 1·7) anti-arrhythmic drugs, one had an anti-tachycardia pacemaker, and one had previous arrhythmia surgery. Thirty seven APs were overt (WPW) with a minimum pre-excited PR RR of 170 to 330, mean 235 ms, and 15 were concealed. Ebstein's anomaly was present in one, other conduction disease in one, and one had a large coronary sinus diverticulum. Patients received two to 43 (mean 12) 500 kHz radiofrequency applications of up to 45 W. Procedure time varied from 80 to 330 (mean 206) min, and fluoroscopy time was eight to 125 (mean 57) min. Success in overt AP was 31/37 (84%), but was only 6/15 (40%) in concealed APs. Overall success was 37/52 (71%) APs, and 33/47 (70%) patients. Left free wall APs were successfully treated in 21/28, 75% (17/20, 85% in WPW), posterior septal in 9/13, 69% (7/9, 78% in WPW), anterior septal in 6/8, 75% (6/6, 100% in WPW), and right free wall in 1/3, 33% (1/2, 50% in WPW). Reasons for failure included a coronary sinus diverticulum in one and complete failure to reach the appropriate part of the atrio-ventricular ring in four. Catheter manipulation was very difficult in several of the other failures—only one size, shape, and reach of deflectable tip catheter was available during this series. There was only one complication, a small pneumothorax after subclavian stab, which was treated medically. Three failures have been treated surgically, two await surgery, one has elected for medical treatment, and eight await another ablation. Patient success has improved from 66% in the first half of patients treated, to 74% in the second half.

Radiofrequency catheter ablation is an increasingly successful treatment for patients with APs.

Clinical experience with selective radiofrequency ablation in the treatment of atrioventricular nodal reentrant tachycardia

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Transcatheter application of radiofrequency current is a technique with sufficient precision to allow selective ablation of slow or fast pathway conduction in patients with atrioventricular nodal reentrant tachycardia (AVNRT). We have attempted selective atrioventricular (AV) nodal modification in seven patients (aged 26–55; all women) with drug-refractory AVNRT. For fast pathway ablation, the catheter was positioned across the tricuspid valve to record the His potential then withdrawn slightly before the application of repeated radiofrequency pulses until persistent PR prolongation was obtained. In the slow pathway technique, mapping was performed along the septal leaflet of the tricuspid valve between the coronary sinus and His region and radiofrequency delivered at sites of possible pathway potentials. Six patients underwent AV nodal modification by the fast pathway approach, receiving 4 to 49 discharges. PR prolongation developed after 13/163 deliveries and transient high grade AV block was seen in 28/163. Mean PR interval was prolonged by 79 (range 60–120) ms and AH interval by 50 (25–95) ms. In four patients, ventriculoatrial conduction was abolished and AVNRT rendered non-inducible. In the other two, AVNRT was still inducible; in these patients, tachycardia persisted despite induction of high grade AV block with further radiofrequency pulses, presumably indicating interruption of AV nodal conduction below the tachycardia circuit; one required a permanent pacemaker. In two patients, slow pathway modification was attempted in the first instance. In one case, AV nodal duality was successfully abolished with no change in PR or AH interval and AVNRT was rendered non-inducible. In the other, this method was unsuccessful but fast pathway modification was subsequently effective. The five patients in whom AV nodal modification was successful by either approach have remained free of AVNRT during follow up 1 to 52 weeks.

Selective radiofrequency modification is an effective treatment for AVNRT. The fast pathway approach, however, may result in interruption of AV nodal conduction below the tachycardia circuit, allowing persistence of tachycardia despite PR prolongation.

Catheter ablation for the cure of atrioventricular nodal reentrant tachycardia by destruction of the slow pathway

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Atrioventricular nodal reentrant tachycardia (AVNRT) is one of the two common mechanisms for paroxysmal supraventricular tachycardia. Its circuit is thought to include a normal AV nodal ("fast") pathway, and an abnormal "slow" pathway. Selective ablation of the slow pathway should provide a physiological cure, whereas fast pathway ablation is associated with complete AV block in up to 10% of cases. We have treated six patients with recurrent AVNRT using radiofrequency ablation of the slow pathway. The patients were all women, aged 14 to 49 (mean 31), with symptom duration of nine to 38 (mean 17) years. Four had suffered syncope, and all had required multiple stays in hospital for their arrhythmias. They had been refractory to one to six (mean 3·7) anti arrhythmic drugs. One had an anti-tachycardia pacemaker. At electrophysiological study, AVNRT was induced in all, and dual anterograde pathway physiology was seen in all but one patient. Mapping was performed with a deflectable tipped, 2 mm spaced, electrode catheter. Slow pathway activity was thought to be evidenced by a discrete electrical potential, between the atrial and ventricular electrograms, always closer to the atrial electrogram, but preceding the His bundle electrogram detected on another catheter electrode. This site was on the inferior margin of Koch's triangle, superior and anterior to the ostium of the coronary sinus, 1 to 2·5 cm distant from the electrode recording the His bundle. At this site 500 kHz radiofrequency energy of up to 45 W was delivered. The patients received four to nine (mean 6·2) bursts of energy. All procedures were performed with local anaesthesia, except in the 14 year old child. In the five patients with demonstrable AH jumps before the procedure, these were abolished in three, and were grossly exaggerated in the other two. At the end of the procedure, AVNRT could not be induced in any of the patients, despite the administration of atropine. Total procedure time, including electrophysiological study, was 135 to 270 (mean 182) minutes, with fluoroscopy times of 17 to 51 (mean 30) minutes. The only complication was a small pericardial effusion in one case, thought to be due to a right ventricular pacing electrode. All patients remain well and symptom free during follow up, except for one, who has had a single recurrence of AVNRT, and is awaiting a second procedure.

Radiofrequency ablation of accessory atrioventricular pathways: which electrogram characteristics are useful in the identification of successful target sites?

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Radiofrequency current represents a safe power source for ablation of accessory pathways (APs) but requires precise mapping for success. Radiofrequency ablation was attempted in 50 patients (age 11 to 66) with 51 APs (seven concealed) to control refractory or life threatening arrhythmias. Locations of APs were left free wall (26), posterior or mid septal (20); anteroseptal (one) and right free wall (four). Conduction was successfully abolished in 46/51 pathways (90%) and has recurred in 3/46 (7%) during follow up of 6 (5) months. Median duration of procedure (including 30 min for observation) was 140 (range 35–360) min and screening time was 44 (4–187) min. The number of radiofrequency pulses varied from one to 51 (median 12) per session. Complications included pericarditis, (three cases) and complete heart block (one case). The optimum mapping criteria for recognition of appropriate target sites have not been established. Accordingly, we analysed the local bipolar electrograms from 406 consecutive sites of radiofrequency delivery in 30 patients with pre-excitation, all recorded via the ablating catheter (4 mm tip, 2·5 mm interelectrode spacing) during anterograde mapping. Local atrioventricular time (A-V), time from delta wave onset to local ventricular activation (QRS-V), and the presence of a possible AP potential were noted. Comparing the 28 successful sites with all 378 unsuccessful sites, A-V time was similar (41 (15) *v* 46 (14) ms; NS), QRS-V was more negative (−3 (11) *v* 10 (15) ms; $p < 0{\cdot}0001$), and AP potentials were commoner (8/28 *v* 27/378; $p < 0.001$), but compared with 38 sites at which transient AP block developed, there were no significant differences in electrogram characteristics. A QRS-V $\leqslant 10$ ms identified successful sites with a sensitivity of 96% but positive predictive accuracy (PPA) was only 9·9%. A QRS-V $\leqslant 0$ ms identified only 75% of successful sites (PPA 12·1%). Combination of QRS-V $\leqslant 10$ ms plus AP potentials was even less sensitive (29%) and only slightly more specific (PPA 23%).

Radiofrequency ablation of APs is safe and effective, but the poor specificity of electrogram characteristics for identifying appropriate target sites contributes to the lengthy procedure times required in some cases.

A novel technique using a bipolar right ventricular/left ventricular electrode configuration for radiofrequency ablation of "difficult" septal pathways

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Although the overall success rate for radiofrequency ablation of accessory pathways is high, particular difficulty may be encountered with accessory pathways located in the anatomically complex posterior septal region, including intermediate septal accessory pathways, some of which require lengthy procedures with increased radiation exposure and yet still result in failure. We describe a new technique for ablation of these "refractory" accessory pathways by delivery of radiofrequency current between sites of early ventricular activation on either side of the septum. This bipolar electrode configuration has been used in eight patients (aged 13–53; six women, two men) with intermediate or posteroseptal accessory pathways (two concealed), two of whom had previously undergone unsuccessful radiofrequency procedures. Ablating catheters (4 mm tip, 2·5 mm spacing) were introduced into the right and left ventricles and the septal region was mapped. Although favourable electrograms could always be recorded from both sides of the septum, multiple (up to 44) unipolar radiofrequency discharges from right or left ventricles to a surface indifferent electrode were ineffective or only produced transient accessory pathway block. By contrast, bipolar radiofrequency delivery between right and left ventricular electrodes permanently abolished accessory pathway conduction in all eight patients within 10 s: in five cases bipolar delivery succeeded with the same electrode positions at which unipolar radiofrequency pulses had failed. The first bipolar pulse was effective in five patients, and five to nine bipolar pulses were required in the other three. The time from delta wave onset to local ventricular activation ranged from -15 to 10 ms at the right ventricular sites and -20 to 0 ms at the left sites. Local atrioventricular times were 30–60 ms in the right ventricle (continuous activity in five of eight electrograms) and 20–65 ms in the left ventricle (continuous activity in four of eight). Accessory pathway conduction has not recurred in any patient during mean follow up of 16 (range two to 22) weeks.

Use of the bipolar right and left ventricular technique may successfully ablate septal accessory pathways where multiple unipolar radiofrequency pulses have been ineffective, and potentially could reduce procedure time, radiation exposure and overall failure rate in these difficult cases.

Detailed mapping of the posteroseptal space for catheter ablation of posteroseptal accessory pathways

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The posteroseptal space has complex anatomical relations and localising accessory pathways in this region is difficult. Between 1988 and 1991 we have undertaken catheter ablation of posteroseptal accessory pathways in 19 patients (12 men, aged 19 to 57, mean 35). All patients had had palpitation (for seven to 24 (mean 15) years), four had been syncopal during tachycardia (two rescued from sudden cardiac death) and all were identified on the basis of standard electrocardiographic appearances and the finding of earliest activation at the mouth of the coronary sinus during previous routine electrophysiological study. At catheter ablation, localisation was performed during atrioventricular re-entrant tachycardia or ventricular pacing in all, and in 15 where pre-excitation was overt, by measurement of local ventricular electrogram to surface delta in sinus rhythm. Detailed recordings were made from the posterior right freewall, post-eustachian space, septal aspect of the tricuspid annulus, and proximal portion of the coronary sinus. When earliest activation occurred in the coronary sinus left sided mapping on the medial aspect of the mitral annulus (MA) was also performed. Coronary sinus angiograms were also obtained; at the site of the pathway there was a stricture in one case, and a diverticulum in another. Lesions were created using low energy direct current in 16 patients and radiofrequency in three and successfully ablated the pathway in 14 (follow up two to 18 median nine months). The ablation site was the posterior right free wall in one, post-eustachian space in three, tricuspid annulus in one, proximal portion of the coronary sinus in six, and a combined proximal portion of the coronary sinus-mitral annulus approach was required in three patients.

Posteroseptal accessory pathways are not uniformly located despite similar electrocardiographic appearances and routine electrophysiological findings. Detailed mapping of the posteroseptal space is feasible and can identify the site of the pathway with sufficient precision to permit successful catheter ablation in most cases.

Endothelium-derived relaxing factor (EDRF) modulates contraction in the intact heart

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Endocardial endothelium modulates myocardial contraction in isolated papillary muscle preparations through the release of a novel contraction prolonging agent, "endocardin", and endothelium-derived relaxing factor (EDRF) that reduces contractile duration, neither agent having any major effect on the early phase of contraction. The influence of EDRF on contraction of the intact heart was investigated. Isolated paced ejecting guinea pig hearts were studied at constant filling pressure and afterload (with 1 μM indomethacin and 0·1 μM acebutolol). Bradykinin (0·1 μmol/l), which releases EDRF from vascular endothelium, shortened the duration of the left ventricular pressure profile without influencing early systole: ejection duration decreased by 6% and cardiac output by 31% ($n = 6$, both $p < 0{\cdot}05$), with no change in peak left ventricular pressure, end diastolic pressure or peak rate of pressure rise. Coronary effluent nitrite concentrations (a measure of EDRF production) increased from 3·7 (0·4) to 6·5 (0·8) nmol/min, and coronary flow from 7·6 (0·9) to 9·2 (1·1) ml/min (both $p < 0{\cdot}05$). When EDRF synthesis was inhibited by 30 μM L-N^G monomethylarginine, all these effects of bradykinin were almost abolished (ejection duration +0·4%, cardiac output +1·3%, coronary nitrite 1·2 (0·2) to 2·2 (0·3) nmol/min).

These data show that EDRF modulates contractile duration in the intact heart as it does in isolated papillary muscle preparations. They suggest a novel regulation of cardiac pump function by the coronary vascular endothelium.

Endothelium-derived factor(s) reduce contraction amplitude of isolated functioning cardiac myocytes

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Recently, the endothelial lining of cardiac muscle has been shown to modulate contraction of isolated papillary muscle preparations, and the contractility of isolated cardiac myocytes can be reduced by the nitric oxide donor, sodium nitroprusside. Furthermore, 5-hydroxytryptamine releases nitric oxide from the coronary microvasculature. We have developed a novel coculture model of functioning cardiac myocytes sited on confluent endothelial cells to investigate whether nitric oxide from endothelium modifies myocyte contractility. Endothelial cells were prepared non-enzymatically from bovine aorta and cultured on glass coverslips. A coverslip was mounted on the stage of an invertd microscope and superfused with Krebs-Henseleit buffer, containing 2 mM calcium, at 32°C. Guinea pig cardiac myocytes were prepared, added to the coverslip, and allowed to adhere to the endothelial cell layer. Contraction amplitude and velocity of shortening of electrically stimulated (0·5 Hz) myocytes were recorded using a videomicroscopy length detection system and analysed by computer signal averaging. Myocyte contraction amplitude was calculated as a percentage of the resting length. Under control conditions myocytes shortened by 5·3% (0·6) (mean (SEM), $n = 12$). Subsequently, 100 mM bradykinin, used to generate nitric oxide from the endothelial cells, reduced myocyte shortening by 10·9 (3·5)% ($n = 12$ experiments; $p < 0{\cdot}03$). This effect was not found in the presence of 10^{-4}M L-nitroarginine methyl ester (L-NAME), an inhibitor of nitric oxide synthesis ($n = 7$). Maximal contraction velocity and relaxation time were not affected. Myocyte contraction was not modified either by the presence of unstimulated endothelium, or by bradykinin alone.

The contraction of cardiac myocytes is modulated by bradykinin stimulated, but not quiescent endothelium. This small effect is abolished by L-NAME, suggesting that the effect is mediated by endothelial cell nitric oxide derived. This interaction may be of importance as there is an intimate relation between the microvasculature and cardiac myocytes.

Modulation of myocardial contraction via activation of K^+ channels by an agent released from coronary vascular endothelium

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The role of the coronary vascular endothelium in the regulation of myocardial contraction was investigated in isolated, externally paced Langendorff perfused ferret hearts. Hearts from pentobarbitone anaethetised ferrets were excised and perfused with Krebs-Henseleit buffer (37°C, 1·25 mM Ca^{2+}; 95% O_2: 5% CO_2) containing 0·01 mM acebutolol and indomethacin. Left ventricular pressure was recorded via a fluid filled latex balloon. Continuous intracoronary infusion of bradykinin (10^{-6}M) induced a transient (two min) reduction in peak pressure of 16·2 (3·6)% and maximum rate of pressure development of 14·7 (2·5)% (both $p > 0{\cdot}05$, $n = 6$; Student's *t* test), associated with a fivefold increase in myocardial cyclic guanosine monophosphate (GMP) concentrations ($n = 6$, $p < 0{\cdot}05$). Earlier 30 min infusion of N^G-nitro L-arginine (10^{-4} M), to inhibit release of endothelium-derived relaxing factor, abolished the elevation of myocardial cyclic GMP concentrations but not the inoptropic response to bradykinin. Earlier bolus injection of 0·1 ml 0·5% triton X-100, to remove endothelium, abolished both the cyclic GMP and inotropic responses to bradykinin. Earlier five min infusion of the K^+-channel blockers glibenclamide (10^{-6} M), or 4-aminopyridine (10^{-3} M) likewise inhibited the inotropic response to bradykinin.

These results suggest that myocardial contractile performance can be influenced by a coronary endothelium-derived factor that acts by opening myocardial K^+ channels.

Mechanism of hypoxic vasorelaxation of precontracted isolated porcine coronary arteries

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Although hypoxic vasodilatation of coronary arteries may be important in sustaining myocardium distal to stenoses, little is known of the mechanism. To study the phenomena we have used 62 porcine coronary artery rings (2 to 5 mm in diameter), the heart was obtained within five minutes of death from nine animals. Rings were studied in duplicate, one with endothelium (E+) and one where endothelium was mechanically removed (E−). The tension was studied isometrically in 20 ml organ baths containing Krebs-Ringer bicarbonate solution at 37°C. Initially 95% O_2 and 5% CO_2 gas mixture was continuously bubbled through the solution giving a Po_2 of 68·4 (2·9) kPa. The rings were precontracted with prostaglandin $F_{2\alpha}$ (10^{-7} to 10^{-5}M) to achieve a stable plateau of contraction by a mean period of 33 minutes. Then rings were treated with nothing (control); N^{ω}-nitro-L-arginine methyl ester (L-NAME) (10^{-4} M), which inhibits nitric oxide synthase; ouabain (10^{-6} M), which inhibits Na^+-K^+-ATPase; tetraethylammonium (TEA) (5×10^{-3} M), which inhibits the voltage dependent K^+ channels or tolbutamide (10^{-4} M), which inhibits ATP-K^+ channels. After achieving a further stable plateau of tension the bubbling gas mixture was switched to 95% N_2 and 5% CO_2 to give a final Po_2 of 8·8 (0·3) kPa and stable relaxation in 46 minutes (range 14–82 min). We have found that hypoxia caused complete relaxation of the control coronary artery rings (113·2 (7·0)% and 114·6 (12·1)% in E+ and E− rings respectively, NS). In comparison with control E+ rings there was a significant reduction in relaxation of rings treated with ouabain (59·4 (7·3)% in E+; $p < 0.001$ and 73·8 (11·0)% in E− rings; $p < 0.01$), TEA (79·6 (7·5)% in E+; $p < 0.01$ and 77·2 (12·9)% in E− rings; $p < 0.02$) and L-NAME (79·9 (11·1)% in E+ rings; $p < 0.02$). There was no significant reduction in hypoxic relaxation of rings treated with tolbutamide (104·5 (13·8)% in E and 93·4 (24·2)% in E− rings).

Going from hyperoxia to hypoxia causes a comparable relaxation of coronary artery rings with and without endothelium. The predominant mechanism involves vascular smooth muscle Na^+-K^+-ATPase and to a lesser degree voltage dependent K^+ channels. Also, in coronary artery rings with endothelium, release of nitric oxide contributes to relaxation.

Nitric oxide (NO) release is responsible for the accommodation of the pulmonary vasculature to increased flow

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It is believed that increased rate of perfusion of the lungs is accommodated by passive recruitment of pulmonary arteries. In large mammals such as humans, sheep, and pigs, nitric oxide is continuously released from pulmonary endothelium and determines the low basal pulmonary arterial tone (Cremona G, *et al. Am Rev Respir Dis* 1991). Here we describe the effects of inhibition of nitric oxide production the adaptation of the vasculature of isolated lungs to increased rate of perfusion. The lungs were "harvested" from eight anaesthetised pathogen free sheep using a method developed to preserve heart and lungs for transplantation (Hakim M *et al, J Cardiovasc Thorac Surg* 1989). The lungs were ventilated with 20% O_2, 5% CO_2 and perfused through a pulmonary artery cannula with either Krebs-dextran (35% dextran and 5% albumin) or autologous blood (mean haematocrit 35%). A Doppler flow probe was used to monitor flow rate into the pulmonary artery and a perfusion pressure was recorded with a transducer connected to a catheter inserted into the pulmonary artery. The perfusate was allowed to drain freely into the venous reservoir kept at constant temperature (37°C), the rate of perfusion being altered by varying the speed of the roller pump. Indomethacin (10^5M) was added to the reservoir in all studies. Blood and Krebs-dextran perfusates were studied with and without pre-treatment with N^{ω}-nitro-L-arginine methyl ester (L-NAME) (10 ^{4} M), which inhibits nitric oxide synthase, and subsequently each was studied after addition of the exogenous nitrovasodilator sodium nitroprusside (10 ^{4} M). A linear relation was found between perfusion pressure and flow rate. The regression of perfusion pressure on flow rate had significantly steeper slopes with blood than Krebs-dextran perfusate (blood 8·7 (0·8); Krebs-dextran 5·15 (0·2), this difference in slope was maintained after L-NAME. Inhibition of nitric oxide production with L-NAME significantly increased the intercept value of pressure at which flow started (Krebs-dextran 0·8 (0·3) to 7·9 (1); blood 3·1 (1) to 8·8 (1·5). In both Krebs-dextran and blood perfused lungs slopes also increased with L-NAME (Krebs-dextran 10 (0·6); blood 13·6 (1). Sodium nitroprusside causes the curves to return to normal.

These data suggest that active release of nitric oxide is a determinant not only of low pulmonary vascular tone but also of the critical opening pressure of pulmonary arteries recruited by increased flow.

Distribution and regulation of binding sites for ^{125}I-calcitonin gene related peptide in bovine coronary arteries

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It is uncertain whether neuropeptides, such as calcitonin gene related peptide (CGRP), exert a significant tonic influence on vascular peptide receptors and if regional variation in the vascular activity of peptides may be due to differences in the distribution of receptors. We have examined the distribution and characteristics of ^{125}I-labelled human CGRP (^{125}I-hCGRP) binding sites in the left anterior descending coronary artery of innervated and denervated bovine hearts. Complete functional denervation of the heart was achieved by a novel cryosurgical technique two to four weeks before excising the heart. Denervation was confirmed by direct nerve stimulation, assaying tissue catecholamine concentrations, and by immunohistochemistry. ^{125}I-hCGRP binding sites were localised and analysed using quantitative in vitro autoradiographic techniques. Specific high affinity (K_d 0·39 nM (95% CI 0·26–0·52 nM) ^{125}I-hCGRP binding sites were localised to the media of both epicardial and intramyocardial bovine coronary arteries. A differential distribution of binding was found, with a higher density of binding sites occurring on distal compared with proximal epicardial regions of the left arterial descending coronary artery ($p = 0.0041$) and on intramyocardial compared with epicardial arteries ($p = 0.0001$). The binding sites exhibited a higher affinity for hCGRP (K 0·85 nM (0·51–1·19) than for $hCGRP_{8-37}$ (K_i 7·49 nM, (4·22–10·76)) and the linear analogue (Cys $(ACM)^{2\cdot7}$) hCGRP (K_i 30·44 nM, (20·84–40·04)), suggesting that they correspond to the $CGRP_1$ receptor subtype. Addition of guanosine-5-O-(3-thiotriphosphate) to the incubation buffer reduced the association and increased the dissociation of ^{125}I-hCGRP binding, indicating that the binding sites are coupled to a guanine nucleotide binding protein. Extrinsic cardiac denervation resulted in a depletion of CGRP-like immunoreactive nerve fibres associated with coronary arteries and an increase in the density ($p = 0.0092$), but not in the affinity of coronary artery ^{125}I-hCGRP binding sites.

The CGRP released from local nerve terminals may exert a tonic influence on coronary artery receptors, and regional variation in the vasodilatory activity of CGRP may reflect a differential distribution of binding sites. It has yet to be determined whether the changes found in binding site density after extrinsic cardiac denervation have a functional consequence.

Radionuclide angiography with a multiwire camera and tantalum-178: an advance over conventional imaging techniques

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This investigation assesses the use of a portable, high speed digital multiwire camera and tantalum-178, a short lived isotope ($t_{\frac{1}{2}}$ = 9·3 min) with significantly improved patient dosimetry over conventional agents, for radionuclide angiography. Tantalum-178 is obtained by elution of a generator system housed within the camera and containing the parent isotope tungsten-178 ($t_{\frac{1}{2}}$ = 22 days) creating a self contained portable imaging system that can be taken to the patient's bedside or to the cardiac catheterisation laboratory in the acute setting. The properties of the camera isotope combination permit the use of larger doses of isotope than with conventional systems while simultaneously decreasing the effective patient radiation dose. As part of the initial assessment of the system, 27 patients underwent supine measurement of ventricular function at rest by gated blood pool imaging with a single crystal camera and technetium-99m, and by first pass angiography using a multiwire camera and tantalum-178. Also, 17 of these patients had first pass angiography using the single crystal camera and technetium-99m. Each patient had all investigations performed within a period of two weeks and with no change in medication. Left ventricular ejection fractions using the multiwire system showed a significant correlation with those obtained by gated blood pool imaging (r = 0·86, p < 0·001), and with those obtained by conventional first pass angiography (r = 0·69, p = 0·002). The correlation coefficient between the conventionally obtained gated blood pool and first pass images was 0·74 (p < 0·001). The average dose of isotope with the multiwire system was 969 MBq and with the conventional system 555 MBq. With the multiwire camera the effective radiation dose was decreased by a factor of 11·4. Average counts in the left ventricular end diastolic frame increased by a factor of 15 with the multiwire camera when compared with conventional first pass angiography (from 374 to 5694).

The multiwire system accurately assesses ventricular function while offering major advantages in terms of improved patient dosimetry.

Assessment of myocardial viability by ^{15}O-labelled water and positron emission tomography (PET) in patients successfully thrombolysed for acute myocardial infarction

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The study aim was to predict the improvement in regional wall motion after successful thrombolysis for an acute myocardial infarction by positron emission tomography (PET). Eleven patients treated with intracoronary thrombolysis were studied in whom vessel patency was confirmed at angiography 24 hours later. Echocardiography and PET studies were performed three to six days after acute myocardial infarction, at which time 14 asynergic segments were identified. Eleven control segments were selected on the basis of having normal wall motion and an angiographically normal arterial supply. Follow up echocardiography was performed four to six months later to assess contractile recovery. The PET imaging protocol consisted of a transmission scan, ^{15}O-labelled carbon monoxide (blood volume) and ^{15}O water emission scans. Regional myocardial blood flow was calculated from the ^{15}O water data set by a previously validated protocol. Manipulation of the above PET data enabled calculation of the perfusable tissue index (PTI) for each myocardial region of interest. The PTI is defined as that proportion of the myocardium within a region of interest that is perfusable by water, and may therefore represent an index of tissue viability. Follow up echocardiography identified 9/14 recovery and 5/14 non-recovery segments. Myocardial blood flow in control regions was 1·02 (0·24) ml/min/g, but was reduced to a similar degree in both the recovery and non-recovery segments (0·68 (0·32) and 0·60 (0·18) ml/min/g, p < 0·02 *v* control). The PTI in the control segments was 0·98 (0·08), indicating that all the myocardium in these regions was perfusable by water. In the non-recovery regions, PTI was 0·53 (0·11) (p < 0·02 *v* control), whereas in the recovery segments PTI was relatively preserved (0·88 (0·10), NS *v* control). In the recovery regions, PTI was always > 0·7 indicating that at least 70% of the myocardium should be perfusable by water to enable contractile recovery.

These data indicate that myocardial blood flow alone is not suitable for assessment of myocardial viability and that PTI may represent a valuable means of predicting improvement in regional wall motion after successful thrombolysis.

Myocardial viability after Q wave infarction: evaluation using early and late thallium reinjection imaging

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Reinjection of thallium after stress and redistribution tomography, improves the detection of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction. The optimal time for imaging after reinjection is unknown because of slow redistribution to ischaemic myocardium. To evaluate the potential of thallium reinjection after acute infarction, and to compare early with late reinjection imaging, 30 patients (age 57 (10) y 35 (7) days after a first transmural myocardial infarction were assessed. All patients underwent exercise thallium tomography with image acquisition immediately after stress, after four hours redistribution, and immediately after reinjection of thallium at rest. In a subset of 15 patients, images were also acquired three hours after reinjection. Nine segments per patient were analysed with a visual grading score of tracer uptake from 1 for absent to 5 for normal. One hundred and twenty nine of 270 segments had stress perfusion defects. Of these, 88 (68%) were fixed, and 41 (32%) showed redistribution at four hours before reinjection. Forty two of the fixed defects (48%) showed an improvement immediately after reinjection. Delayed imaging after reinjection provided additional evidence of reversible ischaemia in only 9/145 (6%) segments.

Imaging early after reinjection detected reversible ischaemia not identified by conventional imaging in 21/30 (70%) patients, and provided the only evidence of reversible ischaemia in five (17%) patients. These findings have important implications when revascularisation is considered. Late imaging after reinjection, although theoretically attractive, is unwarranted.

Differences in regional cardiac autonomic innervation detected by metaiodobenzylguanidine imaging

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Metaiodobenzylguanidine (MIBG) is a noradrenaline analogue that can be used to determine cardiac sympathetic innervation. Cardiac sympathetic dysfunction is thought to be a mechanism accounting for the absence of symptoms in silent ischaemia. We aimed to determine if there are regional differences in cardiac sympathetic innervation and whether it is reduced in silent ischaemia. Patients with angiographic evidence of coronary artery disease and no evidence of infarction were allocated to silent and symptomatic ischaemic groups, on the basis of detectable Holter ischaemia with or without symptoms. Patients with Holter silent ischaemia (group 1, $n = 6$), Holter symptomatic ischaemia (group 2, $n = 6$), and normal controls ($n = 6$) underwent ^{123}-MIBG imaging by planar and single photon emission tomography (SPECT) at four hours. Visual analysis of cardiac planar images was also performed. Cardiac uptake was normalised for liver and quantified per short axis area at the base, mid-ventricle and apex. From base to mid-ventricle, uptake increased in group 1 ($p < 0{\cdot}006$), group 2 ($p < 0{\cdot}01$), and controls ($p < 0{\cdot}004$). From mid-ventricle to apex, uptake increased significantly only in the controls ($p < 0{\cdot}001$). Visual analysis showed greater anterior than inferior ventricular wall uptake in 14 patients. In group 1, anterior ventricular uptake was greater than inferior uptake at the mid-ventricle ($p < 0{\cdot}03$) and apex ($p < 0{\cdot}05$). In group 2, the same relation was shown at mid-ventricle ($p < 0{\cdot}01$) and apex ($p < 0{\cdot}05$). Group 2 patients had a trend towards greater uptake than group 1, significant only at the mid-ventricle ($p < 0{\cdot}05$).

These data suggest that sympathetic innervation is greatest in the mid-ventricle and the apex of the left ventricle. Innervation is also greater in the anterior compared with the inferior. There is indirect evidence of reduced sympathetic innervation in silent ischaemia.

Combined assessment of left ventricular wall motion, ejection fraction, and acute myocardial necrosis with a single dose of technetium-99m antimyosin antibody

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In a prospective study of 26 patients with first Q wave acute myocardial infarction, infarct avid imaging, and radionuclide ventriculography, were performed after injection of technetium-99m (740 MBq) labelled antimyosin within 72 hours of chest pain. The early blood phase of technetium-99m labelled antimyosin was used for equilibrium radionuclide ventriculography in the three standard views. Planar images for the detection of myocardial necrosis were obtained earlier, and at 24 hours, in the same three views. Images were evaluated blind by two experienced physicians. Myocardial antimyosin uptake was seen in 21 out of 26 patients (81%). Radionuclide ventriculography was evaluated in 19 out of 21 patients with positive uptake of antimyosin. Mean (SD) left ventricular ejection fraction was 42 (9)% (range 25%–59%). Wall motion abnormality was present in all the 19 patients and this matched with the location of antimyosin uptake. Seven (47%), however, had wall motion abnormality extending beyond the area of antimyosin uptake which may represent stunned or hibernating myocardium. In a further four (21%) patients, the extent of antimyosin uptake exceeded the area of wall motion abnormality, which may suggest myocardial viability in the area of injury. These data suggest that with a single dose of technetium-99m antimyosin, simultaneous assessment of left ventricular function, and delineation of the extent and location of myocardial necrosis may be achieved, improving prognostic evaluation in patients with acute myocardial infarction.

Technetium-99m tetrofosmin (P53) myocardial perfusion imaging in coronary heart disease: comparison with thallium-201 imaging

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Technetium (Tc)-99m Tetrofosmin (Amersham International) is a lipophilic, cationic diphosphine (technetium-D) that has been developed for myocardial imaging. We have compared Tc-D with thallium (Tl)-201 imaging for the detection of coronary heart disease, and assessed redistribution characteristics of Tc-D. Twenty three patients were injected with Tc-D during bicycle exercise and at rest four hours later. A thallium-201 exercise and redistribution study was also performed. Multiple planar views were obtained at five min, 30 min, two h and four h after injection, and all images were assessed by a blinded panel to score patients with myocardial ischaemia, infarction, or normal scan interpretation. Quantitative defect to normal wall ratio was generated to assess redistribution with technetium-D. Thallium-201 detected myocardial infarction in 13 and reversible ischaemia in nine and a normal scan was found in one patient. Technetium-D detected all correctly except one patient with ischaemia at five min. There was no statistical difference between defect: normal wall ratio between different time points. There was significant increase in lung uptake of thallium-201, but not technetium-D during exercise. Excellent quality diagnostic images were noted as early as five min and up to four h, and there was no evidence of any redistribution with technetium-D. Technetium-D compares well with thallium-201 for the diagnosis of coronary heart disease.

The physical characteristics, low cost, and availability of technetium-ligands make them more attractive for myocardial imaging. Thus technetium-D is a unique, new agent for evaluation of patients with coronary heart disease.

Self-expanding stents for diseased saphenous vein coronary artery bypass grafts

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Dilatation of stenotic segments of saphenous vein coronary artery bypass grafts by conventional balloon angioplasty is associated with a high restenosis rate, which may be more than 60% for lesions involving the proximal graft segment. Intravascular stents may reduce restenosis rates in both native coronary arteries and coronary artery bypass grafts. We have attempted implantation of 91 self-expanding stents into 66 coronary artery bypass grafts in 58 patients (mean age 61) during 68 separate procedures. One stent was implanted in 33 patients, two stents were implanted in 17 patients, and three stents in eight patients. Stent diameter ranged from 3·5 to 6·0 (mean 4·7) mm and stent length from 15 to 30 (mean 24·2) mm. Most stents (62%) were implanted in the body of the graft, but 29% were implanted in the proximal segment, frequently involving the aortic anastamosis. There was failure to deploy the stent in one of the 68 procedures, a procedural success rate of 98·5%, although implantation was difficult in a further nine cases (13%). In hospital occlusion of the stent requiring disobliteration occurred in two cases, with Q wave infarction in one. Bleeding from the femoral puncture site of sufficient severity to warrant transfusion with or without surgical repair occurred after five procedures (7·5%). There was one in hospital sudden death in an elderly patient with poor left ventricular function, and four late deaths (>3 months). Necropsy of two of these four patients showed stent patency. During long-term follow up (mean 11 months) restenosis or occlusion was shown in seven (11%) of stented vessels in seven patients (12·3%), with evidence of myocardial infarction in one. Four patients (7%) have undergone repeat intervention (angioplasty or graft).

Use of the self expanding stent increases the scope of non-surgical treatment of diseased coronary artery bypass grafts, is associated with an acceptable complication rate, and has a much lower restenosis rate than conventional percutaneous transluminary coronary angioplasty.

Experience with the Palmaz-Schatz intracoronary stent

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Intracoronary stents are increasingly used to treat acute dissection and prevent restenosis after percutaneous coronary angioplasty. We have used the Palmaz-Schatz balloon expandable coronary stent in 30 patients. Indications were acute dissection 11 (nine angioplasty, two diagnostic angiography), restenosis seven, vein graft stenosis seven, poor angioplasty result three, ostial stenosis one, and chronic dissection one. Seven were rescue or emergency procedures. A good angiographic result was achieved in all patients but nine technical problems occurred in eight patients; balloon rupture three, vessel dissection proximal to stent site two, thrombosis requiring streptokinase one, misplaced stent two, and dropped stent in coronary artery one. Early complications were few, one patient developed major femoral haematoma due to a displaced collagen plug, and one patient required bypass grafting for acute closure of an undilated vessel. During follow up (0·5–14 months) there have been three deaths; one rescue case died after two days, the other two patients occluded their only supply vessel having had previous restenosis. Twenty three of 27 patients remain asymptomatic, the four symptomatic patients developed restenosis; seven patients had no restenosis at routine re-angiography at six months.

Thus the Palmaz-Schatz coronary stent may be used safely in selected cases, producing excellent angiographic results. We have had no significant acute stent related complications. Late complications are usually heralded by symptoms, whereas asymptomatic patients have had no angiographic restenosis.

Temporary stenting as a bale out procedure during coronary angioplasty

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Autoperfusion balloon catheters that are used to maintain coronary perfusion after inadvertent coronary dissection during coronary balloon angioplasty may limit distal coronary perfusion and obstruct side branches. We have evaluated a temporary stent (Flow Support Catheter, ACS), which provides an internal scaffold to the artery wall when deployed. A radiopaque, braided wire cage, 30 mm in length, and permanently affixed to the distal end of the shaft can be expanded up to a maximum diameter of 4·0 mm and collapsed via a manipulator on the proximal end of the catheter. The shaft of the catheter is a 3·7 French rapid exchange design, allowing the catheter to be deployed over the guide wire. Four patients (age range 41–69) who developed acute coronary dissection during routine balloon angioplasty underwent temporary stenting as an emergency bale out procedure to restore coronary blood flow. Angioplasty was being performed to the left anterior descending coronary artery in three patients and right coronary artery in one patient. Before the temporary stent expansion, flow distal to the dissection was thrombolysis in Myocardial Infarction Trial (TIMI) grades 0–2. During stent expansion (30–209 min) TIMI 3 flow was maintained to both the artery and its side branches covered by the stent. In one patient the device resulted in successful treatment of the dissection, two patients required permanent stenting after its use and in one patient it was used as a bridge to coronary artery surgery. No patient developed enzymatic or electrocardiographic evidence of myocardial infarction after the procedure.

Although worldwide experience of this device is limited, the temporary stent was simple to use and maintained good coronary artery flow while perfusing side branches. The rapidity with which it can be deployed, and its ease of use, make it a useful bale out technique and bridge to other definitive treatment.

Results of stent implantation for the management of aorto-ostial stenosis

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Angioplasty of stenosis in the ostium of the right coronary artery and saphenous vein grafts carry a high rate of complications and restenosis. These may be reduced by the use of intravascular stents. We report the results of aortoostial stenting in 10 patients (nine men), mean age 61 (8). Eight self expanding stents were implanted in saphenous vein grafts and two were implanted in the right coronary artery. Nine were elective procedures. The mean stent length was 27·6 (6·1) mm (range 20–40) and the diameter 5·0 (0·65) mm (range 4·0–5·5). One patient had a slight enzyme rise after procedure and none developed Q wave infarction. There were no in hospital occlusions. A satisfactory primary angiographic result was obtained in all patients. The mean follow up was 16 (12) months (range 4–38). During this time five patients remained symptom free and three others were improved compared with before the procedure. The five symptomatic patients underwent repeat angiography. Of these, two had developed stent restenosis and three had new lesions in other vessels requiring intervention. One patient died from a non-stent related cause.

These preliminary data suggest that stent implantation may be a useful strategy for the management of aorto-ostial stenosis.

Containment of dissection after percutaneous transluminal coronary angioplasty by an implantation of a Palmaz-Schatz coronary artery stent

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Twenty two Palmaz-Schatz coronary stents were implanted in 20 patients (16 men, four women; mean age 53 (range 48–76) to contain dissection after percutaneous transluminal coronary angioplasty (dissection compromising flow 14, dissection with acute occlusion four, dissection with thrombosis two). Percutaneous transluminal coronary angioplasty was performed (left anterior descending coronary artery 13, right coronary artery 7) for severe angina (rest pain in 10, severe exertional angina with positive stress test in five, and chest pain and reversible thallium defect in five). The coronary artery disease comprised 14 stenoses, four chronic occlusions, two stenoses with occlusion (dissection of a normal vessel occurred in one of these). Dissection was successfully contained in 14 patients (one stent in 12 patients, two stents in two), restoring flow: in the remaining six, failure to deliver a stent occurred in two patients, and failure to contain dissection in the other four (three required emergency coronary artery bypass graft). A stent occlusion occurred in five patients (within 24 hours in three, at day five in one, and at day 10 in one) one of whom sustained a myocardial infarction.

Although in most patients, flow threatening dissection after percutaneous transluminary coronary angioplasty can be contained with Palmaz-Schatz coronary artery stents, early occlusion may present a serious problem.

Percutaneous cardiopulmonary support in resuscitation

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Percutaneous cardiopulmonary support has a significant role in the emergency situation. Percutaneous cardiopulmonary support renders haemodynamic stability and maintains perfusion to vital organs thereby enabling intervention to be carried out. Emergency percutaneous cardiopulmonary support was instituted in eight patients (seven men, one woman; mean age 66 range (54 to 82)). Four were in asystole and four were in cardiogenic shock, all after cardiac arrest. Six underwent coronary angiography and subsequent coronary angioplasty, two patients also had intracoronary streptokinase. In two other patients percutaneous cardiopulmonary support was instituted, one after cardiac surgery who could not be removed from bypass, and the other after prolonged resuscitation. Treatment was discontinued as they remained unresponsive with severe left ventricular dyskinesia. In all patients vascular access was obtained by percutaneous cannulation of the femoral vessels using 17f cannulae. The portable percutaneous cardiopulmonary support system consists of a non occlusive vortex pump, heat exchanger, hollow fibre oxygenator, and a control console. Three of the six patients who underwent emergency supported angioplasties survived and were discharged from hospital.

Emergency percutaneous cardiopulmonary support provides a powerful resuscitation tool after which intervention can successfully be undertaken.

Major risk factors for ischaemic heart disease in type 1 (insulin dependent) diabetes: a study of identical twins

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The major cause of excess mortality in insulin dependent diabetes is cardiovascular disease. Potential risk factors for this excess mortality include blood pressure, body mass index, smoking, lipids, lipoproteins, and coagulation factors. Many of these factors are subject to powerful genetic control. Therefore, to establish whether these risk factors are altered by diabetes we studied identical twins discordant for insulin dependent diabetes. Forty five pairs of twins (24 male pairs), mean (SD) age 38 (11) years, mean disease duration 17 (8) years, were selected because they were aged 25 to 85 and without antihypertensive treatment or significantly increased albumin excretion rates, serum creatinine, or hypertension. Non-fasted blood was tested for all risk factors including lipoprotein (*a*) by ELISA (enzyme linked immunosorbent assay), and apolipoproteins (apo), fibrinogen, and factor VII by nephelometric methods. As expected, diabetic twins had significantly higher blood glucose and glycated haemoglobin compared with their non-diabetic co-twins ($p < 0·0001$). Frequency of cigarette smoking was similar in diabetic (33%) and non-diabetic (40%) twins. Genetic influences were probably important for all other risk factors as they were strongly correlated between twins for blood pressure (systolic and diastolic), body mass index, cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglyceride, apo A1 and B, lipoprotein (a), factor VII, and fibrinogen concentrations ($p < 0{\cdot}01$ in all cases). Apo (a) isoforms were identical in twin pairs. There were no significant differences between diabetic and non-diabetic twins for body mass index, diastolic blood pressure, cholesterol, low density lipoprotein cholesterol, triglyceride, apo B, lipoprotein (a), and factor VII concentrations. By contrast, four variables were significantly higher in diabetic twins compared with their non-diabetic co-twins—namely, systolic blood pressure ($p < 0{\cdot}01$), high density lipoprotein cholesterol ($p < 0{\cdot}05$), apo A1 ($p < 0{\cdot}05$), and fibrinogen ($p < 0{\cdot}05$). There was no change in risk factor profile when only 34 twin pairs without retinopathy or microalbuminuria were considered.

The degree of heritability of these cardiovascular risk factors is considerable in patients with diabetes, but diabetes itself adversely affects only blood pressure and fibrinogen concentration.

Snooze-induced excitation of sympathetic triggered activity (SIESTA): the effects of an afternoon nap on the circadian patterns of heart rate and blood pressure

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The surge in ischaemia and onset of myocardial infarction in the morning hours is particularly related to the period after waking and commencing activities. It is suggested that the surge in heart rate and blood pressure at this time is associated with these events. Many people have a siesta in the afternoon (an assumed healthy practice); however, it is not clear whether similar haemodynamic changes occur after such a practice. We performed forty eight hours of ambulatory heart rate and blood pressure monitoring on two consecutive working days in 10 healthy subjects. After a pasta and wine (two glasses) lunch (12 30 hours), subjects were randomised to return immediately to work (13 30 hours) or to a two hour siesta (13 30 hours) lying in a dark room before work, and to alternate the next day. Subjects performed similar activities each evening after work. Heart rate (max, min, mean) was recorded every five minutes during the two days, and blood pressure every 10 minutes from 0600 to 2200 hours and hourly from 2200 to 0600 hours. Circadian patterns were constructed for rate pressure product in addition to individual variables. The rate of change of heart rate and blood pressure after a siesta was similar to that recorded after waking and commencing activities in the morning, and followed appreciable drops in both parameters during the siesta.

It is possible that for those with coronary artery disease, the sudden changes in the determinants of myocardial oxygen demand after a siesta may act as a trigger for cardiac events, much as has been shown in the early hours after waking in the morning.

Dissociation of coronary stenoses progression from changes in left ventricular function in chronic stable angina pectoris

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Although left ventricular function is a major prognostic factor in patients with chronic stable angina, it is uncertain whether left ventricular function deteriorates in the absence of acute myocardial infarction. We studied twenty eight patients with stable angina and angiographically documented coronary artery disease who underwent repeat angiography after a mean (SD) interval of 27·3 (1·3) months. Ejection fraction and percentage severity of stenosis were measured on the first and second angiograms by a computerised system. Stenosis progression was defined as an increase of $\geqslant 20\%$ diameter reduction in a pre-existing stenosis of $\geqslant 50\%$, or an increase of 30% in a pre-existing stenosis $< 50\%$, or any increase in lesion severity that resulted in total coronary occlusion, or a new lesion at second angiography $\geqslant 50\%$. Fifteen of 86 (17·4%) stenoses progressed in 12 patients, (in nine of these (32%) to total or subtotal occlusion). Ejection fraction was unchanged at the time of the first and second angiograms both in patients with stenosis progression and in those without (70·1 (2·2)% *v* 67 (3)% and 68·3 (1·8)% *v* 67·8 (2·1), respectively). In patients with stenosis progression the heart rate blood pressure product at 1 mm ST segment depression during exercise testing, was similar at the time of first and second angiography (204 (26) $\times 10^2$ and 193 (29) $\times 10^2$ beats/min × mm Hg respectively). Increased collateral circulation (grade 3 according to Rentrop scoring) was found in the second angiogram of nine patients who developed total coronary occlusion compared with the first.

In patients with chronic stable angina, coronary stenoses may progress even to total occlusion without clinical deterioration, modification of exercise capacity, or change in the resting left ventricular function. Development of collateral vessels may contribute to the preservation of left ventricular function in patients in whom stenoses progress to total coronary occlusion.

Is life-long anti-arrhythmic therapy necessary to prevent ventricular tachycardia after myocardial infarction?

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It is not known whether it is necessary to continue amiodarone long-term to prevent ventricular tachycardia that has occurred > 10 days after a myocardial infarction. This question is important because of the high incidence of side effects of amiodarone treatment. In this pilot study, amio (200 mg once daily, $n = 7400$ mg once daily $n = 1$) was withdrawn from eight patients, (mean age 63; seven men (range 56–71) after mean 72 (range 46–108 months). Patients were on no other antiarrhythmic drugs and were assessed by electrocardiography, ambulatory monitoring, exercise testing, signal averaged electrocardiogram (SAECG), electrophysiological testing, and drug concentrations. The electrocardiogram showed left bundle branch block in two patients. Left ventricular ejection fraction, assessed by echocardiogram, was <30% in three and >30% in five patients. Ambulatory monitoring showed no VT before stopping amio, at six weeks or at six months after cessation of treatment. Exercise duration at six weeks increased by mean 44% (range 25–90). All had late potentials on SAECG at entry, persisting at six weeks and at six months after stopping treatment. High frequency low amplitude and mean root mean square voltages were unchanged, but QRS duration (ms) shortened between six weeks (unfiltered 129 R103–144, filtered 157 R143–172) and six months (unfiltered 108 R91–126, filtered 135 R120–149). Electrophysiological testing was performed at six weeks (n = 6) and at six months (n = 4). Up to two extrastimuli were used, drive cycle length 600 and 450 ms at the right ventricular apex and in the right ventricular outflow tract. At six weeks, ventricular tachycardia was not inducible in five patients and the ventricular effective refractory period (VERP) was a mean 265 ms (R240–300) at drive cycle length 600 ms. One patient had sustained ventricular tachycardia, was treated with sotolol, and was subsequently non-inducible. At six month mean VERP was 240 ms (R190–260). Amiodarone concentration was 1·1 (0·47) mg/l at entry (n = 8), 0·45 (0·27) at 6 weeks (n = 6) and 0·15 (0·13) (n = 4) at six months. Desethylamiodarone concentration was 1·1 (0·50), 0·67 (0·39), and 0·16 (0·16) respectively. Sleep disturbances were abolished and photosensitivity improved. Thyroid and liver function tests returned to normal. One patient with three previous myocardial infarctions died suddenly at 24 weeks with a fresh myocardial infarction.

These preliminary data show that not all patients with sustained ventricular tachycardia that occurred more than 10 days after a myocardial infarction require life-long antiarrhythmic therapy.

Hypersensitivity reactions to streptokinase in patients with high pretreatment antistreptokinase antibody and neutralisation titres: experience with 189 consecutive patients with suspected myocardial infarction

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Antistreptokinase antibody (AB) and neutralisation titres (NT) can be raised for at least four years after previous streptokinase. No previous study has shown the association of these antibodies to hypersensitivity reactions with streptokinase. We measured pretreatment AB and NT in 189 consecutive patients (mean age (SD) 59 (9·8); 130 men) with suspected myocardial infarction. One hundred and three patients (54·5%) had confirmed myocardial infarction. Fifty seven patients were treated with streptokinase or anistreplase. One hundred and eighty two patients had not received previous streptokinase (mean (SEM) AB, 25 (3), NT, 0·14 (0·08) MU) and seven had (AB 801 (332), NT 3·3 (1·7) MU). Nine of the 182 (4·95%) without previous streptokinase and anistreplase had a raised AB titre of 160 and NT ≥ 0·3 MU. Three patients had documented hypersensitivity reactions to streptokinase. All of these had raised levels of AB and NT. One patient had acute facial flushing and dizziness minutes after streptokinase infusion. His systolic blood pressure later dropped to 70 mm Hg (admission 130/70 mm Hg). He received hydrocortisone and chlorpheniramine before streptokinase. His pre-streptokinase AB was 160 and NT was 0·48 MU. The second patient (AB 160, NT 1·1 MU) did not infarct but received streptokinase. He developed serum sickness with fever, pleural rub, and raised liver enzymes. The third patient's streptokinase was stopped after 150 000 U with a blood pressure drop to 70/40 mm Hg (AB 160, NT 1·5 MU). She developed complete heart block and died from cardiac failure. It is possible that she had an allergic reaction to streptokinase. No patients with low AB or NT had documented reactions with streptokinase. One patient received streptokinase nine months previously, he reinfarcted and received a further dose of streptokinase. His pre-treatment concentrations of both AB and NT were low (AB 10, NT 0·13 MU). He did not suffer an allergic response to the second dose of streptokinase.

High pre-treatment AB and NT are associated with hypersensitivity reactions to streptokinase or anistreplase.

Complications of epidural spinal electrical stimulation (ESES) for angina

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We have implanted epidural spinal electrical stimulation units in 23 patients (aged 46–81) with angina unresponsive to standard medical and surgical treatment. Follow up has been for nine to 50 months. Symptomatic improvement was significant with a change of New York Heart Association grade from a mean 3 (0·75) to 1·85 (0·75) and glyceryltrinitrate consumption fell. These effects were maintained over the follow up period. There were, however, significant complications: (*a*) electrode displacement occurred in 16 patients. Six different types of electrodes were used; the Sigma long displaced eight times in six patients. A new electrode with a spiral S-shape and tines has not displaced (seven patients). (*b*) Fractures of insulation or core occurred nine times in three patients. (*c*) Infections at the site of stimulator implant developed in three and a superficial infection at the site of epidural insertion in one patient. No infections of the epidural space occurred. (*d*) New stimulator units were needed in five because of end of life (one), infection (one), programming failure (two), and elective (one). (*e*) Voltage adjustments and reprogramming were needed in eight patients. (*f*) Two patients died during the follow up period; one during angioplasty and one from cardiogenic shock after a myocardial infarction.

Thus epidural spinal electrical stimulation is a useful technique for the occasional patient with continuing anginal pain despite standard medical and surgical treatments. It appears to be safe but there are complications, with a high incidence of lead displacements. New lead designs may overcome this particular problem.

Reduction of global ventilation-perfusion mismatch is related to exercise capacity in chronic heart failure

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Increased mismatch of ventilation to lung perfusion (V/Q) has been suggested as a possible mechanism for the disproportionate increase in minute ventilation to carbon dioxide production (Vco_2) seen at exercise in patients with chronic heart failure. The inability to match regional lung perfusion to ventilation because of reduced cardiac output has been suggested as one of the limiting factors of exercise in chronic heart failure. To show ventilation to perfusion matching at rest and at peak exercise, eight male patients (mean age 66, range 52–73; mean left ventricular ejection fraction 30%, range 16–45) in New York Heart Association class II underwent maximal symptom limited bicycle ergometry (starting at 50 W, increasing by 10 W min^{-1}). Minute ventilation, VCO_2 and maximal oxygen consumption (Vo_{2max}) were measured from expired gas by mass spectrometry. Vo_{2max} under basal conditions ranged from 11·3 to 24·1 $ml.kg^{-1}.min^{-1}$ (mean 14·6). On separate days, V/Q gamma camera imaging (inhaled krypton-81m gas/intravenous technetium-99m macroaggregated albumin) was performed at rest, and from 80% (previous peak exercise) heart rate during bicycle ergometry. Right lung vertical profiles (normalised to 100% = total lung radioactivity) were subtracted (V-Q) to estimate the vertical distribution of V/Q mismatch. Summed differences (sign ignored) gave a numerical index of global mismatch. A V/Q mismatch was present at rest in all patients. The ability to reduce global V/Q mismatch from rest to peak exercise correlated positively with Vo_{2max} on both treadmill exercise ($r = 0·91$, $p < 0·01$) and bicycle ergometry ($r = 0·89$, $p < 0·01$). The reduction in V/Q mismatch also correlated with the mean arterial pressure at peak exercise ($r = 0·76$, $p < 0·05$), but no correlation was shown with either peak systolic blood pressure, rate pressure product, change in mean arterial pressure from rest or resting left ventricular ejection fraction.

This suggests that the ability to match ventilation to perfusion regionally may be an important determinant of maximal exercise capacity.

Platelet membrane glycoprotein (GPIIb-IIIa) expression and size are increased in acute myocardial infarction

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Platelet aggregation, which plays a pivotal part in acute myocardial infarction (AMI), is mediated by the membrane glycoprotein (GP)IIb-IIIa. This study measured the relative number of GPIIb-IIIa complexes on platelets in AMI compared with control platelets. Blood was sampled within 24 hours of admission and AMI diagnosed by history, electrocardiography, and cardiac enzymes. The control group were admitted at the same time and AMI excluded. Platelet rich plasma was prepared from citrated samples and GPIIb-IIIa quantified using a specific fluorescent antibody and flow cytometry. To eliminate differences in the activation state of the platelets between the groups GPIIb-IIIa was measured before and after stimulation with 0·1 mM adenoside diphosphate (ADP), or the thromboxane mimetic U46619 (1·0 μM). There were, on average, 26% more GPIIb-IIIa complexes on platelets in AMI compared with controls (AMI = 23·7 (1·7), n = 11 and control = 18·8 (1·3), n = 10, arbitrary units $p < 0·05$). Stimulation with ADP or U46619 significantly increased GPIIb-IIIa expression by a similar proportion (22–32%) in each group. Expression of GPIIb-IIIa remained significantly greater in AMI platelets compared with controls ($p < 0·05$ for both ADP and U46619 stimulated platelets). Forward scatter, measured as an index of platelet size, was 15% greater in AMI patients compared with controls (AMI = 4·40 (0·16), control = 3·83 (0·10), $p < 0·05$, arbitrary units).

Platelets in AMI have more GPIIb-IIIa complexes and are larger. As platelet size and protein content are determined at thrombopoiesis these platelets must have been circulating before AMI. Such platelets may be more reactive and, therefore, causally related to AMI.

Circadian variation in white cell aggregation and free radical markers in men with stable ischaemic heart disease

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The fibrinolytic activity of blood has a circadian variation with increased thrombotic tendency in the morning. This may be a contributory factor to the circadian variation in the time of onset of thrombotic events. There has, however, recently been increasing interest into the role of the white blood cell (WBC) and free radicals (FRs) in thrombosis. We have previously reported a circadian variation in WBC aggregation and FR state in normal volunteers. No one has yet studied possible circadian variations in these parameters in patients with stable ischaemic heart disease. Ten men with stable ischaemic heart disease had blood samples collected at four hourly intervals from midday until midday the next day. The patients were ambulant until 00:00 at which time they went to bed and remained in bed until 08:00. The following were measured on each sample: WBC aggregation and malondialdehyde (MDA), which is a product of lipid peroxidation by FRs, the FR scavengers, plasma thiol (PSH), red blood cell glutathione, and superoxide dismutase, which are all altered in the presence of increased FR activity. Aggregation of WBC and PSH concentration had significant circadian variations ($p < 0·015$ and $p < 0·001$ respectively). The WBC aggregation peak was at 12:00 and the trough at 08:00, the PSH peak was at 00:00, and the trough at 04:00. Concentration of MDA did not show any variation. The largest rise in WBC aggregation occurred from 08:00 to 12:00; such an increase in aggregation could predispose to microcirculatory occlusion. The concentration of the scavenger PSH was lowest at 04:00, at this time FR products as measured by MDA in the ischaemic heart disease patients did not fall, this is by contrast with normal volunteers.

This combination of low level of a plasma scavenger and a relatively raised MDA concentration may predispose to thrombosis at this time.

Circadian variation in tissue plasminogen activator, its inhibitor, von Willebrand factor, and prostacyclin stimulating factor in men with stable ischaemic heart disease

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A circadian variation in the fibrinolytic activity of blood has been reported in normal volunteers and patients with myocardial infarcts and unstable angina. This circadian variation in the thrombotic tendency is said to contribute to the increased incidence of thrombotic events in the morning. No one, however, has investigated circadian variations in tissue plasminogen activator antigen (tPA Ag), plasminogen activator inhibitor (PAI), von Willebrand factor (fVIII vWFAg) or prostacyclin stimulating factor (PGI_2SF) in patients with stable ischaemic heart disease. We therefore studied the circadian variation of tPA Ag, PAI, fVIII vWFAg, and PGI_2 concentrations in 10 men with stable ischaemic heart disease on no regular drug treatment. Seven blood samples were collected at four-hourly intervals from 12:00 until the same time the next day. The subjects were ambulant from 08:10 until 00:00 at which time they went to bed. They remained in bed until 08:00 the next morning. Concentrations of PAI had a significant circadian variation ($p < 0·001$), peaks occurred at 04:00 and troughs at 20:00, no significant circadian variations were detected in fVIII vWFAg, or PGI_2 SF concentrations. These results show similar circadian patterns to those of our normal volunteers. Our data indicate, however, for the first time that a significant circadian variation of PAI concentrations exists in patients with stable ischaemic heart disease, which predisposes to thrombosis in the early morning hours.

Furthermore, interestingly, tPA Ag concentrations did not vary significantly during the study period, which is by contrast with the results obtained in normal volunteers. This observation suggests that patients with ischaemic heart disease are at risk early in the morning through both a rise in PAI concentrations and failure of increase in tPA Ag concentrations.

Evidence of free radical production after successful thrombolytic therapy in acute myocardial infarction

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In animal models, myocardial ischaemia and reperfusion are associated with free radical production although the relevance of such studies to the human myocardium is unclear. We have indirectly assessed free radical production after thrombolytic treatment for acute myocardial infarction. Sixty six patients seen within six hours of a myocardial infarction received two bolus injections of alteplase separated by 30 minutes. Coronary artery patency was assessed by angiography 90 minutes after the first bolus. Malondialdehyde (MDA), a marker of lipid peroxidation and the major lipid phase antioxidant vitamin E, were measured at times 0, 30, 60, and 90 minutes, six and 24 hours from 5 ml of venous blood using high performance liquid chromatography. At 90 minutes, a statistically significant rise was seen in mean MDA concentrations compared with baseline (0·91 to 0·99 μmol/l; $p < 0·05$) and a significant fall was seen in mean vitamin E concentration (7·15 to 6·42 μmol/mmol cholesterol) among the 52 patients with thrombolysis in myocardial infarction trial (TIMI) 2 or 3 patency. These results are consistent with significant free radical generation. No significant change was detected amongst the 14 patients with TIMI 0 or 1 patency at 90 minutes.

The potential use of antioxidant agents to modify these changes should be investigated.

Physical training improves skeletal muscle metabolic abnormalities in patients with chronic heart failure: phosphorus-31 magnetic resonance spectroscopy study

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Muscle deconditioning has been considered one of the possible mechanisms for the intrinsic metabolic changes in skeletal muscle in chronic heart failure. To investigate the effects of physical training on skeletal muscle metabolism we studied 12 patients with ischaemic chronic heart failure (New York Heart Association II/III, ejection fraction 24 (3·4)%, aged 62·4 (2·6)). Muscle pH, inorganic phosphate (Pi), phosphocreatine (PCr) utilisation (expressed by the ratio PCr/PCr + Pi), and adenosine diphosphate (ADP) concentrations were evaluated before and after eight weeks of home based bicycle exercise training (20 min/day, six days/week) in a crossover randomised order. Serial ^{31}P spectra of the calf muscle were obtained at rest, throughout plantarflexion at incremental workloads until exhaustion and during the recovery period in both patients and a control group of five age matched healthy men. Training produced an increase in incremental plantarflexion exercise time (9·4 (8) *v* 7·4 (7) min, $p < 0·005$). Utilisation of PCr and concentrations of ADP during exercise were reduced significantly ($p < 0·005$, ANOVA for repeated measures) by training, starting from the first minute (0·81 (0·03) *v* 0·71 (0·02) and 19·6 (4·5) *v* 34·9 (5·1) respectively), at all matched submaximal workloads and even at peak exercise (0·59 (0·05) *v* 0·48 (0·05) and 30·8 (4·3) *v* 51·1 (7·8) respectively). The PCr and ADP recovery half times were significantly faster after training (0·596 (0·1) *v* 0·754 (1), $p < 0·05$ and 0·3 (0·04) *v* 0·41 (0·07) min, $p < 0·05$ respectively). Training produced no significant difference in plantarflexion induced changes in pH. There were no significant differences in PCr and ADP concentrations between chronic heart failure patients after training and controls during the part of the plantarflexion exercise completed by all subjects. There was also no difference in PCr recovery half time between patients after training and controls.

Physical training can reverse the excessive PCr depletion and reduce ADP concentrations during exercise, and accelerate the rate of PCr resynthesis and ADP disappearance during recovery, indicating an improvement in the impaired oxidative metabolism of skeletal muscle seen in chronic heart failure consistent with increased mitochondrial content or improved function of the existing mitochondria.

BRITISH CARDIAC SOCIETY NEWSLETTER

Coronary angioplasty: RITA

We begin our newsletter this month with news of the RITA trials. Those involved will know—but others may not—that RITA is an acronym for Randomised Intervention for Treatment of Angina. We now have two of them so we must speak of RITA-1 and RITA-2. The first trial is a comparison of the efficacy of angioplasty and coronary artery bypass grafting in patients with angina who are considered suitable for either treatment. A total of 1012 patients have been recruited and will be followed for five years. The first analysis will be made after all of them have been followed for at least six months and publication should follow early next year. This is the first major trial that has been supported in part by the British Cardiac Society (other major support came from the British Heart Foundation and from the Department of Health). Our increased activities and expenditure make it unlikely that we will be in a position to offer major support to any other large trial, so that RITA-1 will be unique in this respect at least for the foreseeable future. But we will share the cost (with the British Heart Foundation) of a pilot study for RITA-2 that will compare angioplasty and continued medical care when both are clinically acceptable treatment options. This has been preceded by a feasibility study to ensure that sufficient numbers of suitable patients will be available for the main trial. The news is reassuring: over a two month period 15 centres identified 381 potential participants from 2016 patients who underwent coronary arteriography. The pilot study will have started at Guy's and Wythenshawe by the time we go to press. We seek to recruit 2000 patients over two years. If the experience of the feasibility study can be replicated in most collaborating centres we should attain our target on time. The British Heart Foundation and the Medical Research Council have already agreed to support RITA-2. Additional funding has been promised by industry. RITA-1 and RITA-2 are both important studies that will influence the treatment of angina for many years.

Coronary angioplasty: surveys

Knowing *who* should have an angioplasty is clearly of crucial importance, but knowing *how many* have had an angioplasty is important too. The surveys conducted by the British Cardiovascular Intervention Society (BCIS) have been providing this information in recent years. Data of this type have become essential in these hard days of rigid cost constraint, of providers and purchasers, and of contracts. Good data make a powerful weapon for planning purposes and even the best of cases may seem weak without them. Peter Hubner—the outgoing secretary of BCIS—has given us a progress report on what will be his last survey. "Most of the 1991 annual returns of procedures have been received from the cardiac units. Some, however, are still outstanding: four adult, five private, and two paediatric units have not yet submitted their figures. The European Society of Cardiology has commented favourably on the success of the British audit, but success will be jeopardised if a very high level of cooperation is not maintained. We have some sympathy with the suggestion that centres not participating effectively should be identified in any incomplete report. For the survey to be meaningful, knowledge of those who are contributing and of those who are not may indeed be essential. Be warned . . . Approximately 20 units report on a monthly basis using a faxed return. This simplifies the work of the individual unit and is greatly appreciated by BCIS. We hope that others will adopt this method." While on the topic of BCIS, we recorded Peter Hubner's retirement as secretary in the June newsletter, but failed to note that Martin Rothman had taken over from Man Fai Shiu as chairman. Man Fai has been a pioneer of coronary angioplasty in the United Kingdom. His contributions include invaluable work in assessing resources for angioplasty and in setting educational requirements in this rapidly developing field.

Rationing: age as a criterion for admission to a CCU

We have been surprised recently to hear (indirectly, but from two sources) of junior staff expressing discontent with admission policies for cardiac care units. The complaints were similar: seemingly inflexible admission policies about the age of patients. The matter has also been aired in a recent paper by Dudley and Burns (*Age and Ageing* 1992;21:95). It seems from a postal questionnaire that 20% of cardiac care units operate an age related admission policy and 40% an age related thrombolysis policy. We all understand that some aspects of health care are rationed either implicitly or explicitly and that age is one of the criteria often used in making decisions on who should receive expensive treatment and who should not. But a brief stay on a cardiac care unit over a critical period of myocardial infarction is not unduly expensive. Moreover, risks are greatest in the elderly, and these risks can be reduced to an impressive degree by modern treatment such as thrombolysis (well demonstrated by ISIS-2) and by judicious arrhythmia management. Why should elderly patients be denied such benefits? As taxpayers they have paid their subscriptions.

We believe that admission to a cardiac care unit should be based on likely risk reduction. On that basis, a 73 year old who had an anterior infarct less than an hour age should take precedence over a 45 year old who no longer has symptoms after an uncomplicated small inferior infarct five hours earlier. Would anyone disagree? If not, we could at least claim broad agreement on the principle, while realising that decisions in real life are usually more difficult.

Rationing: how should we do it?

The question of rationing health care is always a difficult one, and it will become more so as technology advances. Many of us—who are conscious of our role as the patients' advocates—would prefer not to make decisions about access to treatment in individual cases. It is easier to live with guidelines set by consensus, and indeed these can enable us more readily to discuss the issue frankly with our patients. Anything less than complete honesty can be a barrier to a good doctor-patient relationship. Not many years ago any talk of rationing would have been frowned upon by those responsible for the service, though even then resources were finite and inadequate: it was convenient to be shielded by the doctors who were left with difficult decisions, especially in the management of elderly patients. Greater realism has been forced upon us, and in some Regions we have already seen the first examples of procedures being made unavailable for the National Health Service. So far these have not been in our specialty and the decisions have not been unduly controversial. But what of the future? Policy decisions on access to treatment *will* be made, either with or without a strong input from the profession. Should we be discussing these issues now so that we are ready to respond? Perhaps this major topic is one for our Medical Practices Committee to ponder. We would be interested in your views, and so would Kim Fox who is the chairman of that committee.

Implantable cardioverter defibrillators

Implantable cardioverter defibrillators provide a good example of modern technology that is not used widely in the United Kingdom because of cost constraints. They can, nevertheless, transform the outlook for patients with life-threatening arrhythmias, and slowly the number of devices is increasing. This trend will continue. A patient booklet has now been published by the British Heart Foundation. It has been written by Anthony Nathan and Maree Barnett from Barts, and can be obtained through Heather Waring who is the education manager at the Foundation (tel: 071 935 0185).

Ambulance paramedical staff and prescription-only medicines

In most areas of the country, ambulance paramedics have been administering drugs as part of emergency care. This has been possible under the vicarious liability of the ambulance authority and of its local paramedic steering committee. The legality of his has been questioned in the past, but it is likely to change. Many readers will know that advice is now given to ambulance services through a Joint Colleges Ambulance Liaison Committee (JALC), representing most of the Royal Colleges and representatives of the ambulance service—with observers from the Department of Health. Discussions between JALC and the then Regional Ambulance Officers resulted in a recommendation for an agreed list of drugs for life-threatening emergencies that might be given by ambulance paramedics acting in their own right. After minor modifications, the list was agreed by the Medicines Control Agency and presented to the Medicines Commission, which has now approved the list. Next it must pass to parliament for an amendment of the Medicines Act. It seems likely that ambulance paramedics will join midwives in having limited powers to give prescription-only medicines. We will bring more news of this—with a list of drugs involved—if the amendment is passed. This may happen within weeks.

News from committees

John Camm has sent a progress report from the committee on radiation hazards in cardiology. "The committee has met and decided to approach the problem under the following sub-headings: local and international standards, equipment and practice, guidelines for good practice, training/audit/supervision, voluntary registrations scheme, angioplasty, catheter ablation, paediatric interventions. The sub-committee will meet again in May or June and a report is expected shortly thereafter. We will be pleased to receive any comments or information."

News of meetings

David Wood has written about a workshop on preventive cardiology. "A one day meeting on preventive cardiology is being organised by the British Cardiac Society's Committee on Epidemiology and Prevention, with the objective of drawing up clinical guidelines on the role of cardiologists at region and district level in strategies for prevention. The meeting will take the form of a workshop with invited cardiologists from every region in the country, and places will be limited to 40. Discussion documents on the potential roles of a cardiologist in relation to primary prevention, on the investigation and management of risk factors in those who have already developed coronary disease, and on the rehabilitation of patients (both medical and surgical) will be circulated in advance and presented at the meeting. Small working groups will then form to agree clinical guidelines on prevention, separately for district and regional cardiologists. These will constitute the basis for the final report with recommendations that we plan to submit for publication in the *British Heart Journal*. The meeting will take place at Fitzroy Square on Wednesday 14 October, 1992."

Readers are urged not to delay in booking places (again restricted to 40) for the teach-in at Fitzroy Square on 10 November. It is being organised by Michael Davies who has chosen the title "Emerging Concepts in the Basic Processes of Atherogenesis". Despite being a didactic session, it will contain hot news, it will be fascinating, and it will be clinically relevant. The details of the programme are still being worked out, but David Leake of the University of Reading will speak on lipid structure and lipid oxidation, and Peter Weissberg on smooth muscle proliferation. As before, the session will start at 10 am and finish by 4 pm for the sake of those who have to travel long distances. Lunch will be provided.

We have received the excellent news from Philip Poole-Wilson that the Congress of the European Society of Cardiology will be held in Britain in 1996. The venue will be Birmingham, the dates 25 to 29 August. This will be a great opportunity for British cardiology, but it will demand considerable thought and careful planning if we are to make the most of it. We have great confidence that it will be a great success. Now that we have at least one centre that can handle the large numbers and all the accoutrements of a major international conference we hope it will be the first of many.

News of colleagues

We have received news of the following new consultant appointments: John Creamer as cardiologist to Stoke on Trent, Jean McEwan as senior lecturer at University College Hospital, Jonathan Fox as physician with an interest in cardiology at Southport Hospital, David Hackett as physician with an interest in cardiology at St Albans and Hemel Hempstead, and Phillip Thomas as physician with an interest in cardiology at Singleton Hospital, Swansea. Finally, we are very pleased to record that Dennis Krikler, immediate past editor of the *British Heart Journal*, and Peter Sleight, immediate past editor of *Cardiovascular Research*, have been awarded British Cardiac Society medals that were made specially for them. The presentation was made to Dennis Krikler at the Society's annual meeting in Harrogate.

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
DUNCAN DYMOND
Secretary, British Cardiac Society,
9 Fitzroy Square,
London W1P 5AH

NOTICE

The 1993 Annual Meeting of the **British Cardiac Society** will take place at the Wembley Conference Centre from 18 to 21 May.

Correction

Strenuous exercise, plasma fibrinogen, and factor VII activity. *J B Connelly, J A Cooper, T W Meade* (May issue, volume 67: pages 351–4). An incorrect result appeared in table 3 of this paper. A correct version of table 3 appears below.

Table 3 Mean values (95% confidence intervals) adjusted for age, smoking, alcohol habit, BMI, and non-manual occupation according to exercise intensity

	Exercise intensity			
	Strenuous (775)	*Mild (2809)*	*None (255)*	*p (F test)*
Fibrinogen (g/l):				
Mean	2·70	2·77	2·76	0·01
95% CI	2·66 to 2·75	2·74 to 2·80	2·70 to 2·82	
VII (% standard):				
Mean	86·5	86·0	88·1	0·35
95% CI	84·6 to 88·4	84·8 to 87·3	85·2 to 91·1	
Systolic blood pressure (mm Hg):				
Mean	135·8	136·0	134·1	0·24
95% CI	134·4 to 137·3	135·0 to 137·0	131·9 to 136·4	
Cholesterol (mmol/l):				
Mean	5·74	5·85	5·87	0·03
95% CI	5·65 to 5·83	5·79 to 5·91	5·74 to 6·01	

BMI, body mass index.

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  R A Daynard
- Support for restricting smoking at workplaces in developing countries: a survey of Peace Corps staff
  T R Eng, S L Emont, T H van der Vlugt

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The length of time a patient's BP is 'in the red' (>140/90 awake, 120/80 asleep) is known as 'BP load'[1]. It is linked to the prevalence of left ventricular hypertrophy – a strong predictor of cardiovascular morbidity and mortality[2].

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Impaired renal function: – May require a lower maintenance dose. 'Zestril' is dialysable.

Elderly patients: – No change from standard recommendations.

CONTRAINDICATIONS: Pregnancy – stop therapy if suspected. Hypersensitivity to 'Zestril'. Patients reacting with angioneurotic oedema to previous ACE inhibitor treatment.

PRECAUTIONS: Assessment of renal function is recommended. Renal insufficiency; renovascular hypertension; surgery/anaesthesia; possibility of hypotension especially in ischaemic heart disease and cerebrovascular disease. Combination with anti-hypertensives may increase hypotensive effect. Sometimes increased blood urea and creatinine and/or cases of renal insufficiency if given with diuretics. Minimises thiazide-induced hypokalaemia and hyperuricaemia. Potassium supplements, potassium-sparing diuretics and potassium-containing salt substitutes not recommended. Indomethacin may reduce hypotensive effect. Possible reduced response in Afro-Caribbean patients. Use with caution in breastfeeding mothers. Do not use in aortic stenosis or outflow tract obstruction or cor pulmonale. Monitor lithium serum levels if lithium salts administered.

SIDE EFFECTS: Dizziness, headache, diarrhoea, fatigue, cough and nausea. Less frequently, rash and asthenia. Rarely, angioneurotic oedema and other hypersensitivity reactions; renal failure; symptomatic hypotension (especially if volume-depleted); severe hypotension (more likely if severe heart failure); palpitation; hyperkalaemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Zestril') and impotence.

PRODUCT LICENCE NUMBERS AND BASIC NHS COSTS: 'Zestril' 2.5mg (29/0208) 28 tablets, £7.84, 5mg (29/0204) 28 tablets, £9.83, 10mg (29/0205) 28 tablets, £12.13, 20mg (29/0206) 28 tablets, £20.96.

'Zestril' is a trademark.

Further information is available from: ICI Pharmaceuticals, King's Court, Water Lane, Wilmslow, Cheshire SK9 5AZ.

REFERENCES: 1. White WB, Dey HM and Schulman P. Am Heart J 1989; **118:** 782-795. **2.** Kannel WB. Am J Med 1983; **75:** 4-11.

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ABBREVIATIONS should *not* be used in the text, except for mathematical calculations and units of measurement.

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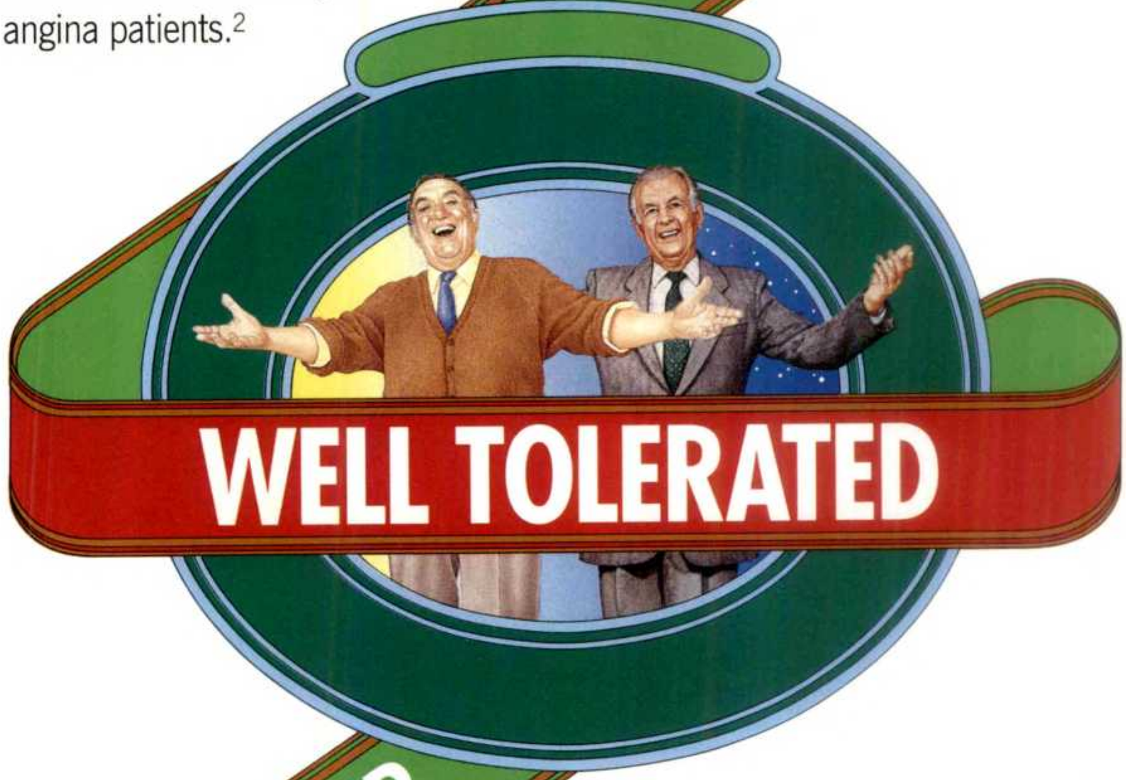

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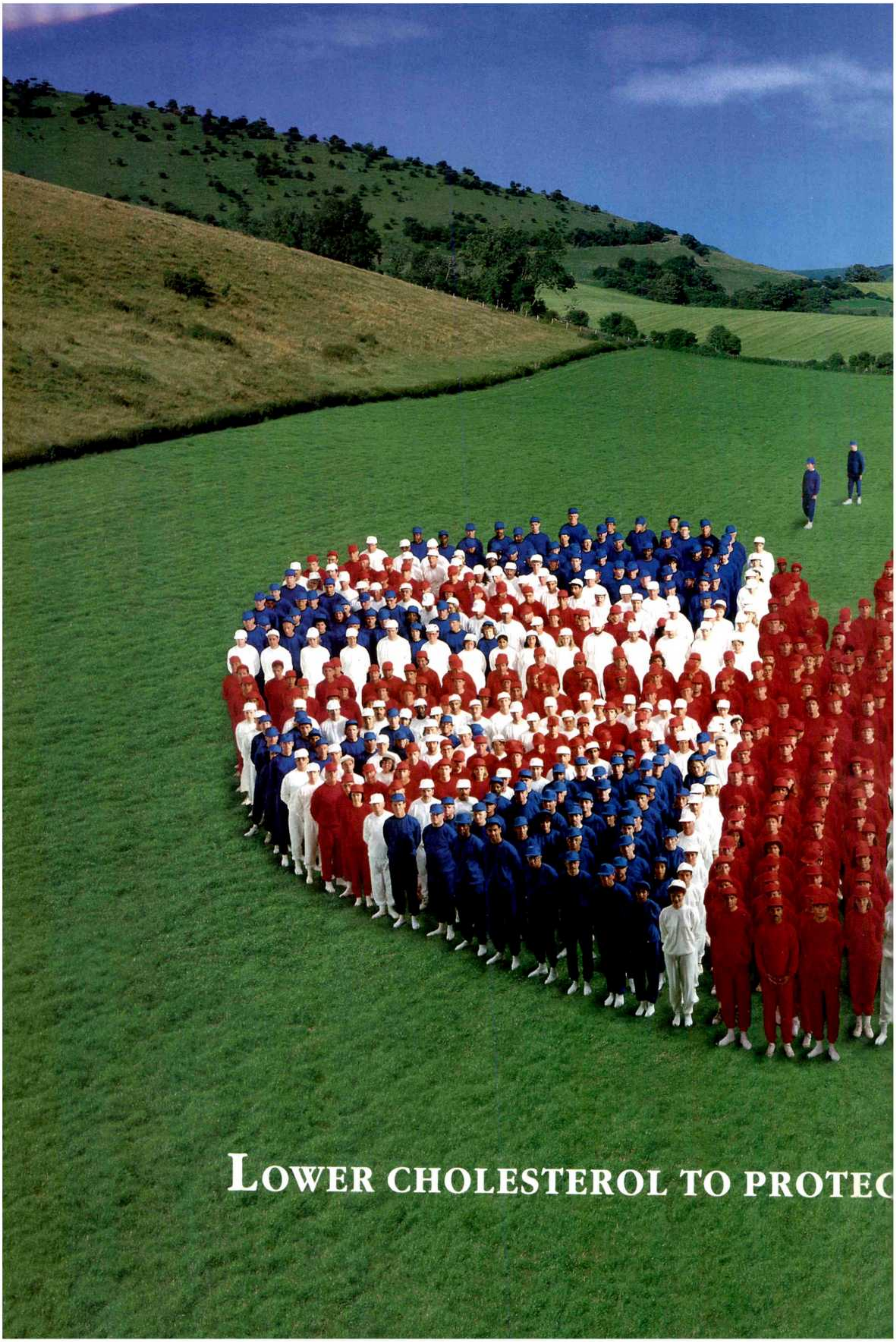
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Editorial

Extending the use of autologous arterial conduits in myocardial revascularisation

Anastomosis of the left internal mammary artery to the left anterior descending coronary artery gives excellent long-term patency and improved early and late survival with few myocardial infarctions and reoperations.[1-3] The advantages of using the internal mammary artery operate irrespective of age, sex, degree of left ventricular dysfunction, pattern of coronary disease, and surgical caseload.[4 5] The apparent benefits of a single internal mammary artery graft made it both inevitable and appropriate that more extensive use of autologous arterial conduits should be evaluated to determine whether it would result in additional improvements in late morbidity and mortality. Use of both internal mammary arteries for grafts, including free and sequential grafts, has been the most commonly applied technique.[6 7] The right gastroepiploic[8] and inferior epigastric arteries[9] have also been used successfully. So far large groups of patients with these alternative conduits have not been evaluated.

The case for the more widespread application of multiple autologous arterial grafts can be considered in three broad areas: (*a*) operative technical factors; (*b*) early morbidity and mortality; and (*c*) late survival of grafts and patients, cardiac events, and freedom from reoperation. If both internal mammary arteries are used, with sequential anastomoses and free grafts[10 11] and lengthening procedures where necessary,[12] multiple distal coronary anastomoses may be fashioned to virtually any point in the coronary system.[13] However, these procedures are technically more demanding and require longer operating times than do single internal mammary artery grafts.[5 7]

The rate of early re-exploration for haemorrhage tended to be increased in the learning period;[14] however, experience and attention to particular aspects of haemostasis reduced this problem.[5 15] The reported association between sternal wound complications and bilateral internal mammary grafting is a major cause of concern.[16-18] Kouchoukos *et al* reported infection rates of 1·9% and 6·9% for single and double mammary grafts respectively.[17] In a prospective study, Grossi *et al* reported similar results.[18] These data contrast with the series from the Cleveland Clinic in which the infection rate was 1% in patients with vein grafts, 0·9% in patients with a single mammary artery graft, and 1·7% when bilateral mammary artery grafts were used.[19] In all these studies,[16-19] however, there was a significant increase in the infection rate in diabetic patients given bilateral mammary artery grafts. It seems possible that the problems of increased pleuro-pulmonary morbidity,[20] chest wall pain,[21] shoulder girdle pain,[22] and brachial plexus injury[23] reported with single mammary artery grafting may increase with widespread use of both mammary arteries.

Because the early mortality for coronary artery surgery is low (2–3%),[24] it is not surprising that the addition of multiple internal mammary artery grafts did not improve survival.[7 25] More noteworthy is that despite the increased complexity of such operations there was no detrimental effect on early survival.[7 25] The possible late benefits of bilateral internal mammary grafts remains to be established.[3 7 10] A prospective trial to compare multiple mammary artery grafting with a single left internal mammary artery to the left anterior descending coronary artery and additional saphenous vein grafts showed no difference in survival at four years.[7] However, in observational studies with a 10–15 year follow up patients with bilateral internal mammary artery grafting had a survival advantage and fewer late cardiac events and reoperations.[2 26] Though these studies may be criticised because of their selection bias and the relatively small numbers, it is nevertheless difficult to ignore these apparent benefits.

The long-term follow up data from the Cleveland Clinic group, whose previous work had such a profound effect on surgical practice worldwide, will be of great interest. Why is the internal mammary artery protected from intimal thickening before as well as after it is used as a bypass graft? Should we expect the same freedom from degeneration and late occlusion in other arterial conduits? The mammary artery has a denser internal elastic lamina that is almost perfectly formed at an early age.[27] It does not show evidence of discontinuities containing smooth muscle cells from the media.[27 28] The media is primarily elastic with scanty smooth muscle cells.[28] Occasional intimal thickening is seen but this usually consists of matrix covered by endothelium.[27] It has been postulated that an internal elastic lamina with no fenestrations can suppress intimal thickening.[27] This may be the basic reason for the longevity of the mammary artery graft. In contrast the internal elastic lamina of the gastroepiploic and the inferior epigastric arteries show fenestrations and the media is rich in smooth muscle cells and relatively poor in elastin.[28] There are fewer discontinuities, however, than in the saphenous vein, which suggests an intermediate tendency for intimal thickening to develop.[27 28]

The low incidence of atherosclerosis in the mammary artery is probably related to its ability to release vasoactive substances[29 30] capable of protecting the vascular wall from platelet adhesion and aggregation and from vasospasm.[31 32] Concentrations of prostacyclin[29] and endothelium derived relaxing factor[30] are higher in the mammary artery than in the saphenous vein. The endothelium of the gastroepiploic artery also secreted more of these vasodilators and inhibitors of platelet activity.[33 34] This may indicate the strong likelihood of an acceptable long-term patency rate for this conduit. There is no information on the biochemical properties of the inferior epigastric arteries.

Advocates of the use of the right gastroepiploic and inferior epigastric arteries showed that these conduits can be used with good early results and minimal increases in operating time and morbidity.[8 9] Though some reservations about a more liberal use of these alternative conduits are warranted their role in routine myocardial revascularisation merits further evaluation. When other autologous conduits are scarce they may prove invaluable.

In 1989 in the United Kingdom less than 4% of patients undergoing myocardial revascularisation had bilateral internal mammary artery grafting whereas 60% had single internal mammary artery grafting.[23] No information is available on the use of the gastroepiploic and inferior epigastric arteries. Widespread use of arterial conduits depends on the long-term survival and freedom from angina and reoperation after their use. This information can only be obtained by careful audit of surgical results and appropriate clinical trials. This may provide the necessary stimulus to surgeons and hospitals to accept the increased complexity, operation time, and surgical expertise required to extend the use of autologous arterial conduits in myocardial revascularisation.

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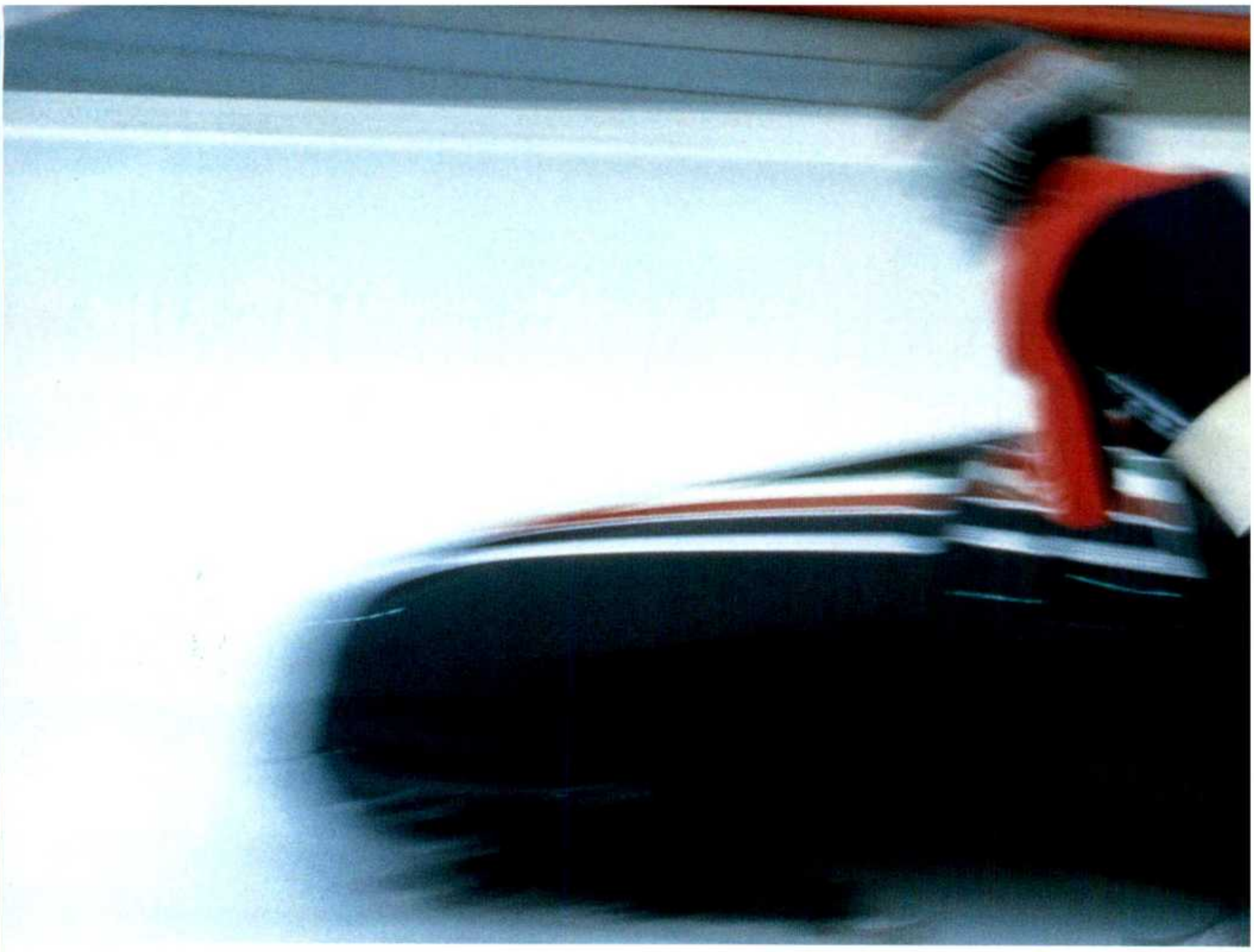

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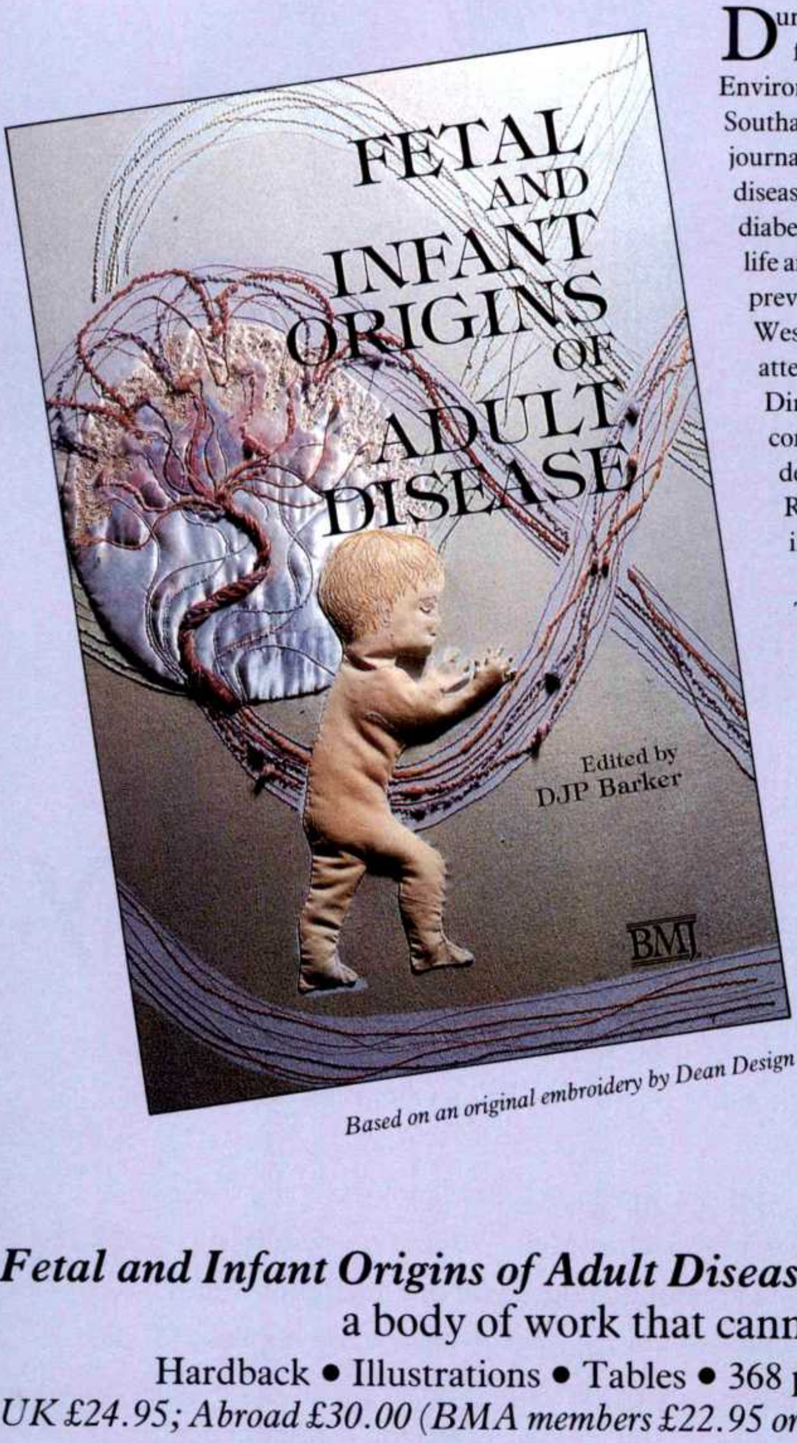

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VIEWPOINT

Pacemaker syndrome: an iatrogenic condition

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Pacemaker syndrome was first described in 1969 by Mitsui when it was referred to as the pacemaking syndrome.[1] The name pacemaker syndrome was first coined by Erbel (using the German Schrittmacher syndrom) in 1979.[2] It can present with symptoms as severe as syncope, presyncope, oedema, dyspnoea, and chest pain, or more moderately and subtly as lethargy, palpitation, or an awareness of venous pulsation all of which may occur when there is atrial systole during ventricular systole. This is most frequent when there is ventriculoatrial conduction from the paced ventricle to the atrium usually via the atrioventricular node.[3 4] The symptoms can be identical to those prompting implant.[5] Occasionally pacemaker syndrome can occur in the absence of ventriculoatrial conduction when ventricular pacing is in competition with sinus rhythm.[6]

Incidence of pacemaker syndrome

The incidence of pacemaker syndrome varies with the vigour with which it is sought and it probably affects 7% of all ventricularly paced patients in its severe form in which it is essential to revise the pacemaker. If mild to moderate symptoms are considered it affects 20% of the ventricularly paced. This group too can benefit clinically from pacemaker upgrade.[7] All too often the symptoms and signs of the syndrome are not sought and patients who previously experienced syncope, now relieved, complain little. This leads to a widespread impression that the syndrome is rare.

Clinical diagnosis of pacemaker syndrome

The diagnosis is made by reproduction of symptoms during ventricular pacing and depends on the history and the search for hypotension, signs of congestive cardiac failure, and venous cannon waves associated with ventricular pacing. Usually the diagnosis can be made clinically without recourse to special investigations. However, Doppler echocardiography can be useful in its diagnosis: Doppler ultrasound measurement of cardiac output in nine patients with ventriculoatrial conduction or symptoms consistent with pacemaker syndrome showed a 30% improvement when fully automatic (DDD) pacing rather than ventricular inhibited (VVI) pacing was used. In the remaining 20 patients with no history of pacemaker syndrome or ventriculoatrial conduction Doppler derived cardiac output improved by 14% when pacing was changed to DDD from VVI.[8]

Haemodynamics of pacemaker syndrome

Contraction of the atria against closed atrioventricular valves during ventricular systole leads to raised atrial pressures, loss of atrial contribution to ventricular filling, and a consequent fall in cardiac output which causes a fall in arterial pressure if the baroreceptor mediated rise in systemic vascular resistance is insufficient.[9] In a study on 20 open-chest dogs with experimental complete heart block left atrial angiography showed retrograde blood flow into the pulmonary venous system at atrioventricular intervals of −50 and −100 ms. Therefore in addition to the loss of atrial contribution to ventricular filling there is a "negative atrial kick" further compromising haemodynamic function.[10] In three patients studied by Alicandri *et al*[11] there was an absent or smaller rise in peripheral resistance in response to a fall in cardiac output. The mechanism was thought to be due to vasodilatation in response to activation of atrial stretch receptors by atrial cannon waves which dominated over the baroreceptor mediated increase in resistance that occurs secondary to the fall in systemic arterial pressure. Similar findings were observed in a group of 20 patients studied haemodynamically more than 24 hours after coronary artery bypass grafting or aortic valve replacement. Hypotension with ventricular pacing occurred only in those patients with left atrial cannon waves.[12] It has been suggested that patients with left ventricular disease, especially hypertrophy of any cause, are more sensitive to the correct timing of atrial systole and are, therefore more liable to be symptomatic with retrograde atrioventricular conduction.[7]

A recent study of a large group of patients with intact ventriculoatrial conduction showed similar results, with peripheral resistance failing to rise in seven patients requiring upgrade to dual chamber mode because of symptoms of pacemaker syndrome whereas it rose during ventricular pacing in the symptom free group.[13] The difference between the response of the cardiac output between the two groups was negligible and the authors argued that the behaviour of the blood pressure was crucial. They advised that a cuff recording of blood pressure should be made at the onset of ventricular pacing during pacemaker implant and that a fall in systolic pressure of greater than 25 mm Hg should be regarded as predictive for the possible development of pacemaker syndrome and they recommended dual chamber pacing.[13] We suggest that if clinicians allow their choice of pacing mode to be guided by haemodynamic variables during temporary ventricular pacing before implant, they must assess the patient in the upright posture (60° head up tilt with appropriate safety restraint) before considering it appropriate to implant a VVI unit.[14]

Pacemaker syndrome in different pacing modes

In a small group of patients, paced in VVI mode and presenting with symptoms of pacemaker syndrome, changing the mode from VVI to atrial inhibited (AAI) relieved symptoms and was associated with a fall in both the mean right atrial and pulmonary capillary wedge pressures as well as a rise in cardiac output.[15] In view of the high prevalence of ventriculoatrial conduction in patients with sinus node disease, AAI pacing with the possible addition of a sensor-driven facility for those patients who do not show an increase in sinus rate on exertion (chronotropic incompetence) is advocated by some for all patients in whom atrioventricular conduction is sound.[16]

Two large randomised controlled trials to compare ventricular and dual chamber pacing in patients with sinus rhythm identified improved well-being even in "asymptomatic" patients when the dual chamber mode was used.[17 18] However, ventricular pacing is the preferred mode in patients with symptomatic bradycardia in the presence of atrial fibrillation.

Although the early dual chamber pacing mode (atrial synchronous ventricular inhibited (VDD)) was an improvement over the atrioventricular sequential (DVI) mode, it was still associated with pacemaker syndrome in those patients whose sinus rate dropped below the programmed lower rate at which point the pacing mode effectively became VVI.[19] With the advent of fully automatic dual chamber pacing systems (DDD) it became apparent that pacemaker syndrome can still occur in properly functioning dual chamber pacing systems in the DDD mode if the atrioventricular delay is programmed either too short or too long.[20] The importance of the timing of left atrial depolarisation was addressed in a study of 16 patients with dual chamber pacemakers who had haemodynamic variables measured at different atrioventricular delays when they were supine and erect.[21] A wide range of interatrial conduction delay (70 ms–380 ms using oesophageal recording) between right atrial pacing artefact and left atrial depolarisation was seen and the optimal atrioventricular delay was more easily identified during 80° head up tilt than with the patient supine. In those patients in whom the interatrial conduction delay exceeded 150 ms (three of 16 patients) a programmed atrioventricular delay of 150 ms resulted in left atrial activation after the ventricular spike, yielding left atrial contraction during left ventricular systole. The temporal difference between sensing of spontaneous right atrial activation and right atrial pacing is such that at a given atrioventricular interval, the sequence between atrial and ventricular contraction is longer in the atrial synchronous ventricular inhibited (VDD) than in the atrioventricular sequential mode (DVI). Some pacemakers now take this delay into account as a programmable feature. The DDI mode has been recommended for patients with carotid sinus syndrome, malignant vasovagal syndrome, and sick sinus syndrome who do not require atrial tracking (ventricular pacing as a result of atrial sensing) and who often have ventriculoatrial conduction.[22–24] In this mode it is impossible for pacemaker mediated tachycardia to occur but pacemaker syndrome can occur with non-conducted premature atrial beats or with retrograde conduction from premature ventricular beats.[25] Either of these events will inhibit atrial output if they occur outside the post ventricular atrial refractory period. They are then followed by a ventricular stimulus at the programmed ventricular rate which may be conducted retrogradely if the atrium has had sufficient time to recover. Ventricular pacing will only then be inhibited if the sinus rate recovers and is normally conducted. In patients with documented ventriculoatrial conduction the atrial refractory period in DDI should be programmed long enough to include the retrograde conduction interval. Thus sensing of a retrograde P wave and atrial output inhibition is avoided. It is suggested that the atrial refractory period be set to 325 ms at programmed rates of 55–85 pulses per minute (ppm), shorter for faster rates, and longer for slower rates.

Pacemaker syndrome in rate responsive pacing

Sensor driven ventricular pacing (VVIR) would be expected to result in pacemaker syndrome at resting heart rates in the same way as non-sensor driven ventricular pacing. In patients with sinus node chronotropic incompetence, a group of patients who are often considered suitable for the VVIR mode, ventricular pacing is often programmed so as to be inhibited at rest but triggered by the sensor during exercise. This may result in pacemaker syndrome during exercise with retrograde atrial activation as the rate of the paced rhythm exceeds that of the intrinsic rhythm.[26] Syncope on exercise has been reported even in the absence of regular ventriculoatrial conduction.[27]

Sensor driven AAI pacing causing pacemaker syndrome—The onset of pacemaker syndrome was reported during exercise in a patient with a dual atrioventricular nodal pathway in whom conduction through the fast anterograde pathway was prolonged to such an extent by concomitant therapy with disopyramide that conduction occurred over the slow pathway.[28] This resulted in pacemaker syndrome during moderate exercise when the paced atrial event was conducted with a long spike Q interval leading to atrial systole just after the preceding QRS during ventricular systole.

Treatment of pacemaker syndrome

Because symptoms of pacemaker syndrome overlap with those of pacemaker malfunction it is vital to exclude malfunction as the first step in investigation. Optimal therapy for symptomatic bradycardia of any cause is use of a pacing system that includes atrial sensing and pacing wherever atrial electrophysiology permits. In practice this will frequently be a dual chamber device where the atrial refractory period should be programmed to at least 25% longer than the measured ventriculoatrial conduction time to avoid pacemaker mediated or endless loop reentry tachycardia. Furman's group evaluated ventriculoatrial conduction in 432 patients receiving a permanent pacemaker.[29] One hundred and sixty two had intact ventriculoatrial conduction including 14% of patients with complete anterograde atrioventricular block. Most patients with intact anterograde conduction had ventriculoatrial conduction. They evaluated these patients by means of incremental ventricular pacing and observed that the ventriculoatrial conduction interval was prolonged in most at faster rates with complete retrograde ventriculoatrial block at rates exceeding 120 pulses per minute in 50% of patients with intact atrioventricular conduction at rest. They estimated that programming the postventricular atrial refractory period to 300 ms, an upper rate limit of 140 ppm and an atrioventricular delay of 125 ms would prevent endless loop tachycardia in 90% of their patients.

Pacemaker syndrome can be avoided prospectively by choice of the most physiologically appropriate pacing mode for the individual patient. While this will inevitably lead to a higher incidence of dual chamber pacing and increased cost, the cost of upgrading as many as 20% of ventricularly paced patients must be considered together with the technical difficulties of passing a second lead and the increased risk of infection that is attendant upon second and subsequent pacemaker procedures. Increased cost need not be enormous if AAI pacing is considered as first choice mode for patients with sick sinus syndrome. Furthermore, the cost of many excellent dual chamber units has now fallen to within the range of many of the most sophisticated single chamber units. If improved physiological performance of dual chamber pacemakers with well demonstrated improved quality of life[17 18] is ignored and patients most likely to have retrograde conduction are targeted the increased cost is moderate and comparable with the need for VVI upgrade. VVI pacing can still be considered for patients who are mostly in sinus rhythm and only show rare episodes of conduction defect and also for patients who are either severely disabled and show no retrograde conduction or who have a poor prognosis because of another disease.

As the use of dual chamber pacing systems with the ability to sense P waves and at least one other physiological variable (by means of sensors such as those for respiratory minute volume and QT interval) increases, a far lower incidence of pacemaker syndrome should result. Furthermore, development of pacemaker artificial intelligence to diagnose the syndrome and automatic adjustment of the pacing mode to avoid it is expected within a few years.

Alternatives to dual chamber pacing therapy of pacemaker syndrome

(*a*) If pacemaker syndrome is encountered, it may be ameliorated by reducing the pacing rate so that competition between sinus rhythm and pacing is minimal with the possible addition of rate hysteresis in which pacing will only be triggered after a pause significantly longer than the pacing interval.[30]

(*b*) Antiarrhythmic drugs may be used to block retrograde atrioventricular conduction. Flecainide has previously been used for this purpose but in the light of the CAST study we do not think that it can be recommended.[31] It and other antiarrhythmic drugs can also paradoxically result in artificial circus movement tachycardias by prolonging the retrograde atrio-ventricular conduction time without complete retrograde block and may result in a retrograde P wave occurring outside the atrial refractory period thereby precipitating pacemaker mediated tachycardia.[32]

(*c*) In those patients who are not pacemaker dependent and in whom the pre-implant symptoms are minor serious consideration should be given to the device being turned off and subsequently, if appropriate, explanted.

New approach to the identification of potential pacemaker syndrome

If a policy of DDD pacing for all suitable patients is not adopted a reliable test to identify patients at risk of developing pacemaker syndrome would be clinically valuable.

Atrial natriuretic peptide was discovered in 1981 and is released directly into the circulation in response to atrial wall stretch within the heart and it has potent vasodilator properties in addition to natriuretic and diuretic ones.[33] Peripheral venous plasma atrial natriuretic peptide concentrations were measured in patients with DDD and VVI pacemakers and they were significantly lower in both the short and long term when the DDD mode was in operation and the concentrations were similar to those observed in controls.[34] This difference is maintained during exercise.[35] Concentrations of atrial natriuretic peptide were lower at physiological delays than at either long or short atrioventricular delays.[36] Atrial natriuretic peptide concentrations were measured in patients with ventriculoatrial conduction both with and without symptoms of pacemaker syndrome. Concentrations were normal during sinus rhythm or DDD pacing (atrioventricular delay 150 ms) in patients with pacemaker syndrome but rose to 7–8 fold during ventricular pacing with intact ventriculoatrial conduction.[37] These data prompt reconsideration of the mechanism of hypotension in pacemaker syndrome. Animal studies[38] (which have not been reproduced by others[39]) offer only weak support to the suggestions of Alicandri *et al*,[11] Erlebacher *et al*,[12] and Witte *et al*,[13] that the mechanism is an exaggerated or inappropriate neural reflex. Atrial natriuretic peptide has well defined vasodilator properties at concentrations seen in patients with symptomatic pacemaker syndrome. These effects may be additive to the neural reflex or may be the sole mechanism of inappropriate vasodilation. The higher concentrations found in patients with symptomatic pacemaker syndrome compared with those who had retrograde atrioventricular conduction without symptoms supports the involvement of an endocrine mechanism in this syndrome.

Pacemaker syndrome particularly in its milder form probably has a higher incidence and prevalence than is currently realised. It may be avoided by carefully programmed dual chamber pacing for all patients with normal atrial activity and atrioventricular conduction disease and by atrial pacing in patients with intact atrioventricular conduction. Pacemaker upgrade should be avoided on grounds of patient discomfort (including infection risk), operator difficulty in passing a second lead, and cost. Thus a policy of VVI pacing for all is no longer tenable.

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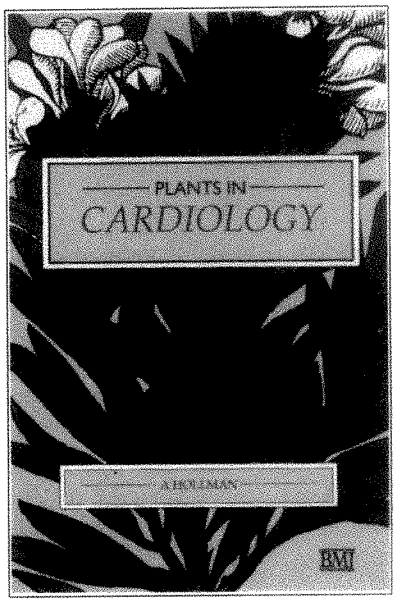

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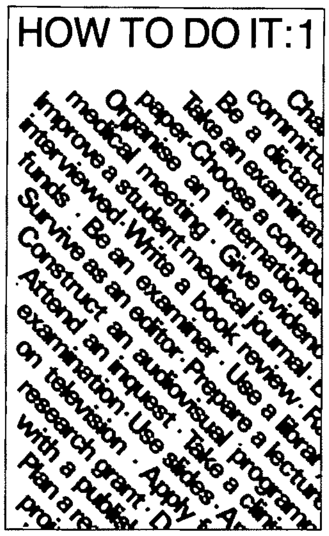

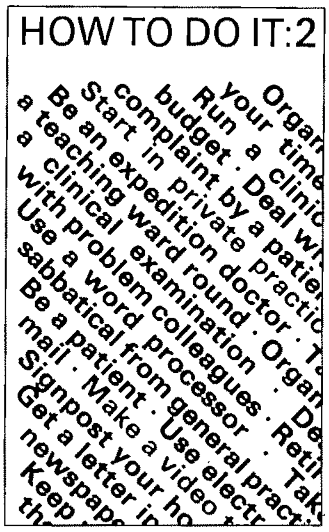

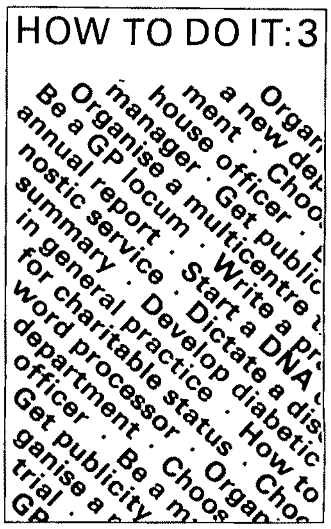

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Br Heart J 1992;68:167–70

Monitoring of streptokinase resistance titre in acute myocardial infarction patients up to 30 months after giving streptokinase or anistreplase and related studies to measure specific antistreptokinase IgG

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Abstract

***Objective*—To examine the induction of antistreptokinase antibodies after giving streptokinase or anistreplase to patients with acute myocardial infarction.**

***Design*—Patients were randomly allocated to receive either $1\cdot5 \times 10^6$ IU, streptokinase or 30U anistreplase in a double blind study. Blood samples were collected immediately before treatment and subsequently at intervals up to 30 months; plasma samples were assayed for streptokinase resistance titre (functional assay) and streptokinase binding by IgG (microradioimmunoassay).**

***Setting*—Cardiology department in a general hospital.**

***Patients*—128 consecutive eligible patients. Samples were collected for up to one year according to a prospective design: a subsection of 47 patients was selected for intensive study over the first 14 days. After one year, all available patients (67) were sampled on one further occasion.**

***Results*—Antibody responses to streptokinase and anistreplase were similar. Streptokinase resistance titres exceeded pretreatment concentrations five days after dosing, and values peaked at 14 days. By 12 months after dosing, 92% of resistance titres ($n = 84$) had returned to within the pretreatment range. Antistreptokinase IgG concentrations also exceeded baseline concentrations within five days and peaked at 14 days. Half of the individual values had returned to within the pretreatment range by 12 months ($n = 84$) and 89% by 30 months ($n = 18$).**

***Conclusion*—Although we cannot be sure of the clinical significance, because of the increased likelihood of resistance due to antistreptokinase antibody, streptokinase and anistreplase may not be effective if administered more than five days after an earlier dose of streptokinase or anistreplase, particularly between five days and 12 months, and increased antistreptokinase antibody may increase the risk of allergic-type reactions.**

(*Br Heart J* 1992;68:167–70)

Varying concentrations of antibodies to streptokinase (SK) may be present in patients with acute myocardial infarction (AMI) as a result of previous streptococcal infections.[1,2] The induction of anti-streptokinase (anti-SK) antibodies after the administration of SK or anistreplase (Eminase, APSAC) is, therefore, an anamnestic response. Previous studies on SK have measured the antibody response with a surrogate endpoint, the functional SK resistance titre, which also reflects the influence of inhibitors such as α_2 antiplasmin and variations in other plasma proteins such as fibrinogen and plasminogen.[1,3,4,5] These studies have shown that a peak value was reached by two weeks after dosing with SK and returned towards pretreatment values by six months.

The development of neutralising antibodies may influence the efficacy and risk of an adverse reaction to SK or anistreplase on readministration for a subsequent myocardial infarction, and in the context of the increasing use of thrombolytic therapy this might become an increasingly relevant clinical problem. It is therefore important to define the times of induction and decline in a population large enough to reflect the range of individual variations in neutralising antibody concentration. It was the purpose of the present work to compare changes in SK resistance titre in response to the standard doses of SK and anistreplase in patients with AMI. The results from this functional assay were compared with those from a novel method of assaying one antibody class (IgG) in terms of antigen binding.[6]

Patients and methods

PATIENTS

One hundred and twenty eight consecutive eligible patients (101 men, 27 women age range 31–70) were recruited between April 1987 and January 1989. Inclusion and exclusion criteria and adjunct treatments have been described previously.[7] Patients were randomised in double blind, double dummy fashion to receive either $1\cdot5 \times 10^6$IU SK infused intravenously over one hour or 30 U anistreplase injected intravenously over five minutes. Initial patency, rates of reocclusion, and adverse events are described elsewhere.[7]

Evaluation of variations in streptokinase resistance titre after dosing with streptokinase or anistreplase

	Period of follow up (months with range)					
Analysis	*3*	*6*	*12 (11–15)*	*18 (16–20)*	*24 (21–27)*	*30 (28–31)*
Median evaluation as fold increase over individual pretreatment value (n)	20 (39)†	15 (38)	4 (60)	5 (22)	2 (20)	2 (18)
Values (%) returning to:						
Within pretreatment range	51	72	92	100	100	100
Within 95th percentile pretreatment range	31	44	76	86	77	88
For all patients (n)	(45)†	(50)	(84)	(22)	(26)	(18)
Theoretical neutralisation of streptokinase (IU) (combining group median)*	$1\cdot2 \times 10^6$	$1\cdot2 \times 10^6$	6×10^5	3×10^5	3×10^5	3×10^5

*Theoretical neutralisation by pretreatment median value = $1\cdot5 \times 10^5$ (assuming a standard plasma volume of 3l).
†Numbers of patients in the two types of analysis differ because median evaluation could only be calculated for those patients for whom pre and post treatment pairs of samples were available. At any one sampling time these pairs of samples are fewer than the total number of patients sampled.

Blood samples were collected from patients before dosing and serially at intervals for up to one year in a prospectively designed study. A subsection of 47 patients was selected for intensive study over the first 14 days although not all samples were received from each patient. Figures 1 and 3 show data from this cohort. The remaining figures and tables show available data for all patients. After one year all available patients (67) were sampled on one further occasion and these patients were grouped according to the classification described in the table.

LABORATORY ASSESSMENTS

The SK resistance titre and antiSK IgG concentrations were measured in individual plasma samples as described previously.[6] Calculations of the theoretical neutralisation of a second dose of SK were performed by multiplying the SK resistance titre by the average plasma volume of 3 litres.

STATISTICAL ANALYSIS

The SK resistance titres and anti-SK IgG concentrations, as analysed by either the Wilk-Shapiro or the Kolmogorov-Smirnov test, were not normally distributed and so cannot be represented as arithmetic means. Values for SK resistance titres and for comparison IgG are shown as median values with ranges. The IgG values have also been analysed as geometric means as the log transformed values are normally distributed, and the conclusions are similar to those derived from a consideration of median values. The SK resistance and antiSK IgG results were analysed by the Mann-Whitney U test.

Results

SK RESISTANCE TITRE

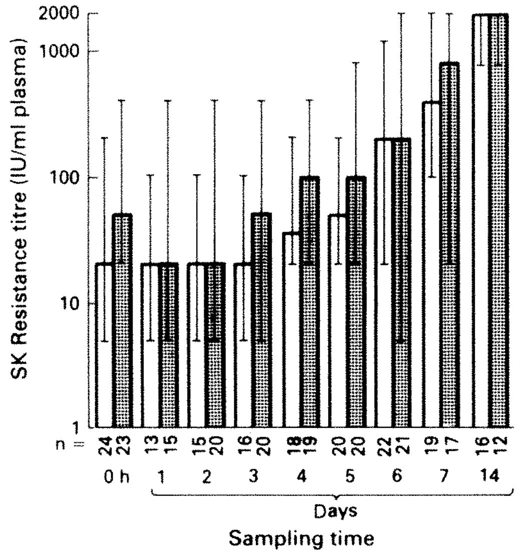
Early serial changes (one to 14 days) were studied in detail in a subgroup of 47 patients. The response was similar whether patients were treated with SK or anistreplase, and baseline (pretreatment) values were consistently exceeded by five days after dosing (fig 1).

Figure 2 shows results for all patients, monitored up to 30 months. Measurements up to 12 months are serial analyses in the same patients (although a maximum of only 84 out of a possible 115 samples were collected in the prospectively designed study). By contrast, each patient was only sampled once over the period 12–30 months; that is, different patients appear in the groups collated at 18, 24, and 30 months and therefore groups are smaller at these times. Sampling times for the points within the period 12–30 months represent ranges: the total ranges are specified in the table.

Changes in SK resistance titre were similar for SK and anistreplase throughout the period of follow up (fig 2). Baseline (pretreatment) values however were significantly higher in the group of patients assigned to treatment with anistreplase (50 *v* 20 IU/ml, $p < 0\cdot05$).

Peak titres were reached two weeks after

Figure 1 Initial changes in SK resistance titre. Values are shown as median and range for patients who received SK (open bars) or anistreplase (stippled bars). Patient numbers are indicated (n).



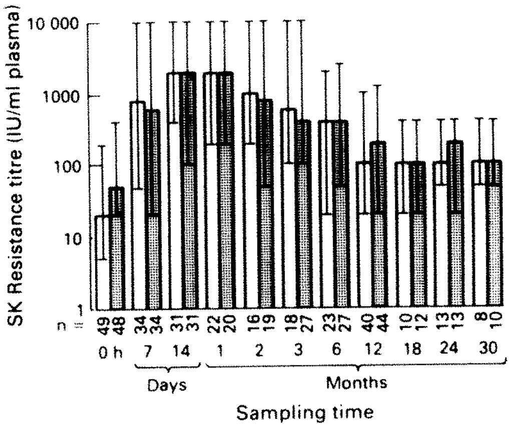


Figure 2 Changes in SK resistance titre up to 30 months. See legend to fig 1 for details.

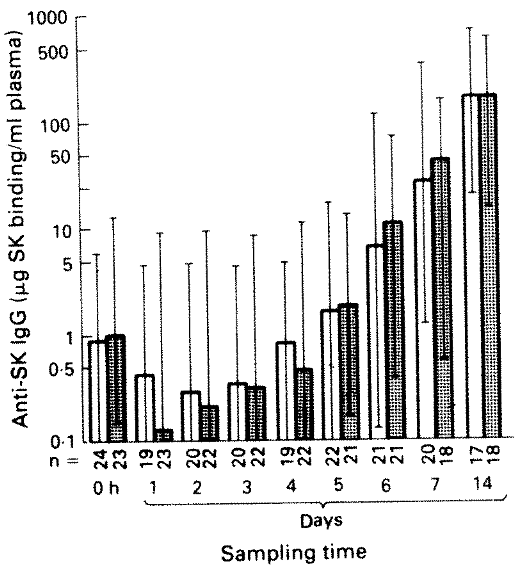


Figure 3 Initial changes in anti-SK IgG. See legend to fig 1 for details.

dosing (40 fold rise in median). Concentrations declined considerably by three to six months (fig 2), although the median rise above individual pretreatment concentrations was still noticeable for those patients in whom a complete set of data was collected (table). When examining all the data, it was seen that most individual values had returned to within the normal (pretreatment) range by six months, most values returned to within the 95th percentile of pretreatment range by 12 months (table). When the values for combined median SK resistance titre (as described in the methods) were used to calculate the theoretical neutralisation of a second dose of SK (assuming a standard plasma volume of 3 l) it was found that most of a standard dose ($1·5 \times 10^6$ IU) might be neutralised up to six months but not thereafter.

ANTISK IGG

The early antiSK IgG response was also similar whether patients were treated with SK or anistreplase (fig 3). There was an initial fall in antiSK IgG in agreement with previous results[2] because of sequestration as the antibody antigen complex but, thereafter, values were restored to baseline by day 5. This early fall in IgG (fig 3) is not accompanied by a similar decline in SK resistance titre (fig 1).

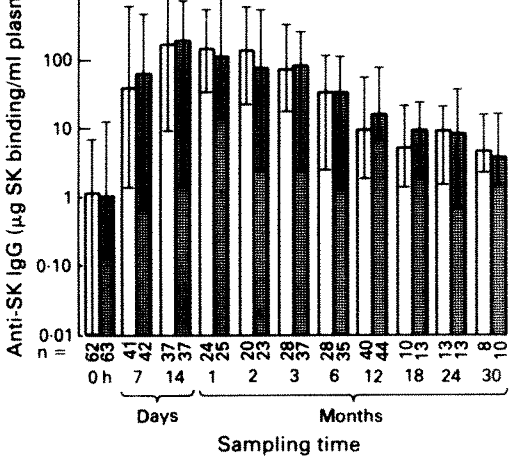


Figure 4 Changes in anti-SK IgG up to 30 months after dosing. See legend to fig 1 for details.

Figure 4 showed results for all patients monitored up to 30 months: changes in anti-SK IgG were similar for SK and anistreplase throughout the period of follow up. It is noteworthy that baseline values are not higher in the patients assigned to anistreplase, unlike the situation with SK resistance titre (fig 2).

In agreement with the changes in SK resistance titre, peak values of anti-SK IgG were attained 14 days after dosing (150 fold rise in median). The subsequent decline in anti-SK IgG, however, seemed somewhat slower than the decline in SK resistance titre: 48% of individual anti-SK IgG values returned to within the normal range by 12 months after dosing (14% at six months, 61% at 18 months, 65% at 24 months, and 89% at 30 months).

Discussion

We have shown already that the range of concentrations of anti-SK antibodies found in AMI populations before first treatment—whether measured specifically as IgG or as the functional SK resistance titre—does not usually influence the thrombolytic efficacy of SK and anistreplase or the incidence of side effects.[2 8] The concentration of antibody is usually low by comparison with the concentration required to bind all SK or anistreplase used,[2 9 10] and the inhibition of lysis is much less than the extent of binding.[2 9]

We have now shown that high values of neutralising antibody are rapidly induced after dosing with anistreplase and SK and the two agents seem to be indistinguishable. When measured in terms of the functional SK resistance titre, the present results confirm and extend previous findings, showing that most values return to within the normal range by six to 12 months. Extrapolating from group SK resistance titres to calculate how much of a second dose of SK might be neutralised, opinions on the possibility of readministration have varied from three months to greater than six months.[1 3 4 5] Our results suggest that much of a second standard dose ($1·5 \times 10^6$ IU) of SK might be neutralised up to six months after the first dose but not at 12 months.

Our assay for specific anti-SK IgG is novel and these are the first results to define the rate of induction and decline after dosing with SK or anistreplase. The incremental change from baseline to two months appears similar to the preliminary results on SK published recently for an enzyme linked immunosorbent assay (ELISA) method.[11] The initial production of IgG, however, appeared to be more rapid when measured by ELISA than by radioimmunoassay in the present or a previous study.[2] At the very high concentrations reached in the first few months, anti-SK IgG is a major contributor to the functional SK resistance titre. The fall in IgG during the first four days after treatment is not accompanied, however, by a reduction in SK resistance titre presumably because the fibrinolytic assay reflects the changes in fibrinogen, plasminogen, and α_2-antiplasmin. The significantly higher baseline SK resistance titre in anistreplase treated patients and the poor correlation between changes in anti-SK IgG and SK resistance from three months onwards may also reflect contributions other than anti-SK IgG, possibly α_2 antiplasmin.

Anti-SK IgG antibodies have occasionally been implicated in adverse reactions after thrombolytic therapy with SK.[11] In view of the very low incidence of severe allergic-type reactions in the large mortality trials of anistreplase[12] and SK,[13,14] however, it is not clear whether an appreciable risk is incurred when IgG is higher. The concentrations of anti-SK IgG in the few patients in our study who showed an allergic-like response[7] were not appreciably different from the concentrations in patients without a response.

There are few publications on the size of the increment in clinically diagnosed allergic-type reactions in response to other antigens when IgG is raised. Work on dextrans indicates that most reactions seen when the IgG antibody titre increases beyond a range of 10 fold from the normal median are likely to be mild (grade I); more severe reactions require a much higher antibody concentration.[15] Furthermore, although serious allergic type reactions are mediated by the complement pathway, complement is also lysed by plasmin in response to plasminogen activators such as alteplase.[16] Therefore, complement activation and any contingent leucocyte attraction may occur regardless of the concentrations of anti-SK IgG.

In conclusion, we have defined the induction of neutralising antibodies to SK and anistreplase in AMI patients with the standard functional assay of SK resistance titre.[1,3,4,5] The responses to anistreplase and SK are similar. Because of the increased likelihood of resistance due to anti-SK antibody, SK, and anistreplase may not be effective if administered more than five days after earlier SK or anistreplase particularly between five days and 12 months, and increased anti-SK antibody concentrations may increase the risk of allergic-type reactions.

We thank Drs E S Johnson, R Cregeen, and Mr S R Hasler for helpful discussions, Nadia James for typing the manuscript, and Julie Hearn for data entry.

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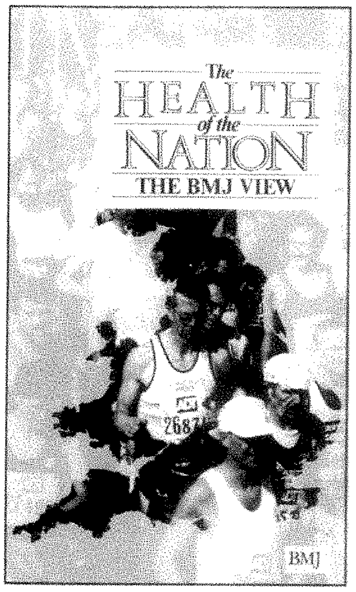
EDITED BY RICHARD SMITH, EDITOR OF THE BMJ



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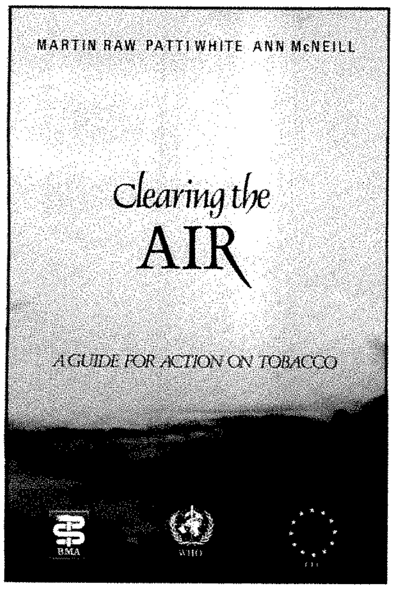
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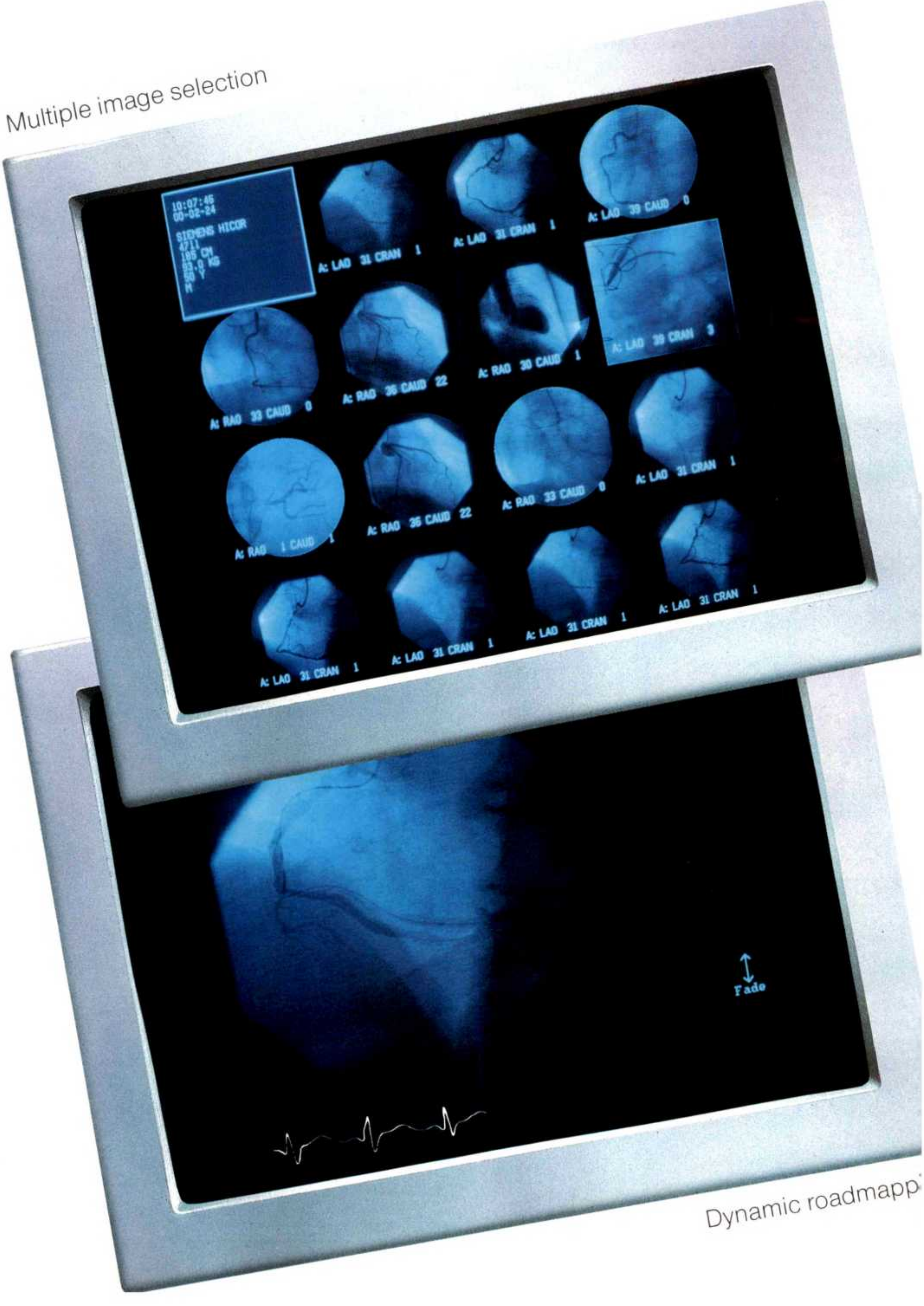

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Br Heart J 1992;68:171-5

Streptokinase induced defibrination assessed by thrombin time: effects on residual coronary stenosis and left ventricular ejection fraction

Kulasegaram Ranjadayalan, Robert Stevenson, Bradley Marchant,
Velaitham Umachandran, Simon W Davies, Denise Syndercombe-Court,
Charles N Gutteridge, Adam D Timmis

Abstract

***Objective*—To evaluate laboratory markers of defibrination early after thrombolytic therapy and to determine their relation to residual stenosis and left ventricular ejection fraction measured angiographically before discharge from hospital.**

***Design*—Prospective analysis of defibrination after streptokinase measured by fibrinogen assay and thrombin time to provide a comparison of these coagulation variables for predicting angiographic responses to treatment in patients with acute myocardial infarction.**

***Setting*—The coronary care unit of a district general hospital.**

***Patients*—44 patients with acute myocardial infarction treated by streptokinase infusion, all of whom underwent paired blood sampling before and one hour after streptokinase and cardiac catheterisation at a median of six (interquartile range 3–9) days later.**

***Main outcome measures*—Assay of thrombin time and plasma fibrinogen concentrations one hour after streptokinase infusion. Relations between these coagulation variables and residual stenosis in the infarct related coronary artery and left ventricular ejection fraction. Separate analyses are presented for all patients (n = 44) and those with patency of the infarct related artery (n = 35).**

***Results*—Streptokinase infusion produced profound defibrination in every patient as shown by changes in thrombin time and circulating fibrinogen. Thrombin time after streptokinase infusion correlated significantly with both residual stenosis ($r = -0{\cdot}43$, $p < 0{\cdot}005$) and left ventricular ejection fraction ($r = 0{\cdot}38$, $p < 0{\cdot}02$). The importance of these correlations was emphasised by the interquartile group comparison which showed that a thrombin time $\geqslant 49$ seconds predicted a residual stenosis of 74% and an ejection fraction of 65%, compared with 90% and 49% for a thrombin time $\leqslant 31$ seconds ($p < 0{\cdot}01$). When the analysis was restricted to patients with patency of the infarct related artery, the correlation between thrombin time and residual stenosis remained significant and group comparisons continued to show that patients in the highest quartile range had more widely patent arteries and better preservation of ejection fraction. Analysis of the fibrinogen data, on the other hand, showed insignificant or only marginally significant correlations with these angiographic variables.**

***Conclusions*—Early after streptokinase infusion for acute myocardial infarction, the level of defibrination measured by thrombin time has an important influence on residual coronary stenosis and left ventricular ejection fraction at discharge from hospital, values above 49 seconds being associated with the best angiographic result.**

(*Br Heart J* 1992;68:171–5)

Reduction in circulating fibrinogen has been regarded as a major requirement for successful thrombolytic therapy and some,[1 2] though not all,[3] investigators have confirmed that high residual plasma concentrations are often associated with non-patency of the infarct related coronary artery. Non-patency of the infarct related coronary artery at discharge from hospital has an adverse effect on one year mortality,[4] and there is an empirical but unproved assumption that a high grade residual stenosis may also increase the risk of recurrent events. Left ventricular ejection fraction at discharge from hospital is recognised as an important determinant of long term outcome,[5 6] but it remains unknown to what extent these angiographic variables are affected by the level of defibrination after thrombolytic therapy. The purpose of our study, therefore, was to evaluate laboratory markers of defibrination early after thrombolytic therapy and to determine their relation to residual stenosis and left ventricular ejection fraction found before discharge from hospital. Defibrination was estimated by fibrinogen assay and also by thrombin time (a measure of the functional integrity of circulating fibrinogen) to provide a comparison of these coagulation variables for predicting angiographic responses to infusion of streptokinase.[7]

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Patients and methods

PATIENTS

Table 1 shows demographic data of the patients. We studied 44 patients with acute myocardial infarction treated with 1·5 mU of streptokinase infused intravenously over one hour. Two hours after completion of streptokinase, the patients were anticoagulated with heparin infused at 1000 units/hour for 48 hours and thereafter were started on 75 mg of aspirin daily according to treatment policy at the time this study was undertaken.

BLOOD SAMPLING AND ANALYSIS

Paired venous blood samples were taken immediately before streptokinase infusion and again one hour afterwards, before infusion of heparin had been started. Samples were drawn without venous occlusion, anticoagulated in sodium citrate, centrifuged, and the plasma frozen to −20°C within 30 minutes of drawing the blood. The plasma was thereafter stored at −80°C until analysis in one batch for measurement of fibrinogen concentration and thrombin time. Fibrinogen was measured by the method of Clauss[8] and thrombin time by automated photodensitometry in an ACL-2000.

CARDIAC CATHETERISATION

All patients gave written informed consent for cardiac catheterisation by either Judkins or Sones techniques involving coronary arteriography with at least five views of the left system and three of the right, and single plane (right anterior oblique) left ventriculography. Studies were performed at a median of six (interquartile range 3–9) days after hospital admission to determine the patency of the infarct related coronary artery, the degree of residual stenosis, and left ventricular function. The infarct related artery was identified as the artery subtending the ventriculographic dyskinetic segment that corresponded to the area of acute injury on the admission electrocardiogram. In this study we encountered no ambiguity between circumflex and right coronary arteries in patients with inferior infarction. The coronary lesions were analysed for patency by two experienced observers (ADT, RS), the quantitative analysis being performed by RS alone. Both observers were blinded to the results of the coagulation analysis. For quantitative analysis, two views were selected that were most nearly orthogonal to the diseased segment and to one another with the least overlap of other coronary branches. The two views were projected with magnification onto white paper and traced by hand. Patency of the infarct related coronary artery was assessed by the thrombolysis in myocardial infarction (TIMI) criteria.[9] Residual stenosis was taken at the narrowest point within the lesion related to the calibre of the normal segment immediately proximal to the lesion. The interobserver reproducibility of this technique has previously been reported.[10] Left ventricular ejection fraction was measured by the method of Sandler and Dodge.[11]

Table 1 Patient characteristics

Characteristic	*No*	
No of patients	44	
Age (median (interquartile range)) (y)	59	(52–65)
Sex		
Men	36	
Women	8	
Infarct location		
Anterior	22	
Inferior	22	
History of previous infarction	5	
Time to streptokinase (median (interquartile range)) (min)	210	(155–278)
Time to cardiac catheterisation (median (interquartile range)) (days)	6	(3–9)
Infarct related coronary artery		
Patent	35	
Non-patent	9	
Coronary artery disease		
Single vessel	18	
Multivessel	26	
Left ventricular ejection fraction (median (interquartile range)) (%)	58	(50–62)

STATISTICAL ANALYSIS

In all analyses, non-parametric statistics were used. Averaged values are expressed as median with the interquartile range in parentheses. Unpaired comparisons were made with the Mann-Whitney U test, paired comparisons with the Wilcoxon test, and correlations were examined with the Spearman rank correlation coefficient. Statistical significance was taken as $p \leqslant 0{\cdot}05$ although marginal values ($>0{\cdot}05$–$<0{\cdot}1$) have been recorded in the manuscript.

Results

RESPONSES TO STREPTOKINASE

Streptokinase infusion produced profound defibrination in every patient as reflected by reductions in circulating fibrinogen and increases in thrombin time. Bleeding complications occurred in two patients, one of whom suffered gastrointestinal haemorrhage requiring blood transfusion and the other frank haematuria. In both cases the baseline fibrinogen concentrations were high (3·7 and 4·0 g/l) compared with the remainder of the group, and showed an exaggerated decline (−3·6 and −3·9 g/l) in response to streptokinase. Table 2 shows responses to streptokinase.

DEFIBRINATION AND CORONARY PATENCY

Coronary arteriography after three to nine days showed patency of the infarct related artery in 35 cases (80%). Comparison of coagulation variables in patients with and without coronary artery patency showed no significant differences. Quantitative analysis, however, of the degree of residual stenosis (range 39%–100%) showed a highly significant correlation with the thrombin time one hour after streptokinase. When analysis was confined to the 35 patients with patency of the infarct related artery, the correlation between residual stenosis (range 39%–99%) and thrombin time remained statistically significant. Correlations with circulating fibrinogen, on the other hand, were not significant.

The relation between defibrination and the efficacy of treatment is emphasised in figures 1 and 2 where residual stenoses of patients in the

Table 2 Coagulation variables before and one hour after streptokinase infusion

	Before streptokinase (median (interquartile range))	*1 hour after streptokinase (median (interquartile range))*	*p Value*
Fibrinogen (g/l)	2·8 (2·3–3·3)	0·21 (0·16–0·27)	<0·001
Thrombin time (s)	13·7 (11·6–15·7)	37·1 (30·7–48·9)	<0·001

highest and lowest quartile ranges for thrombin time and fibrinogen are compared. Patients in the highest quartile range for thrombin time had more widely patent arteries with significantly less severe residual stenoses than patients in the lowest quartile range, regardless of whether the analysis included all patients (fig 1) or only those with a patent infarct related artery (fig 2). Fibrinogen analysis, on the other hand, was less helpful and failed to separate patients on the basis of residual stenosis.

DEFIBRINATION AND LEFT VENTRICULAR EJECTION FRACTION

Defibrination after streptokinase was an important determinant of residual left ventricular ejection fraction shortly before discharge from hospital. Thus the thrombin time one hour after treatment correlated significantly with left ventricular ejection fraction, although when the analysis was confined to patients with a patent infarct related artery the correlation was weaker and just failed to reach statistical significance (table 3). Nevertheless, the interquartile group comparisons confirmed that patients in the highest range for thrombin time had significantly better preservation of left ventricular ejection fraction than patients in the lowest range, regardless of whether all patients were included or only those with a patent infarct related artery (figs 1 and 2).

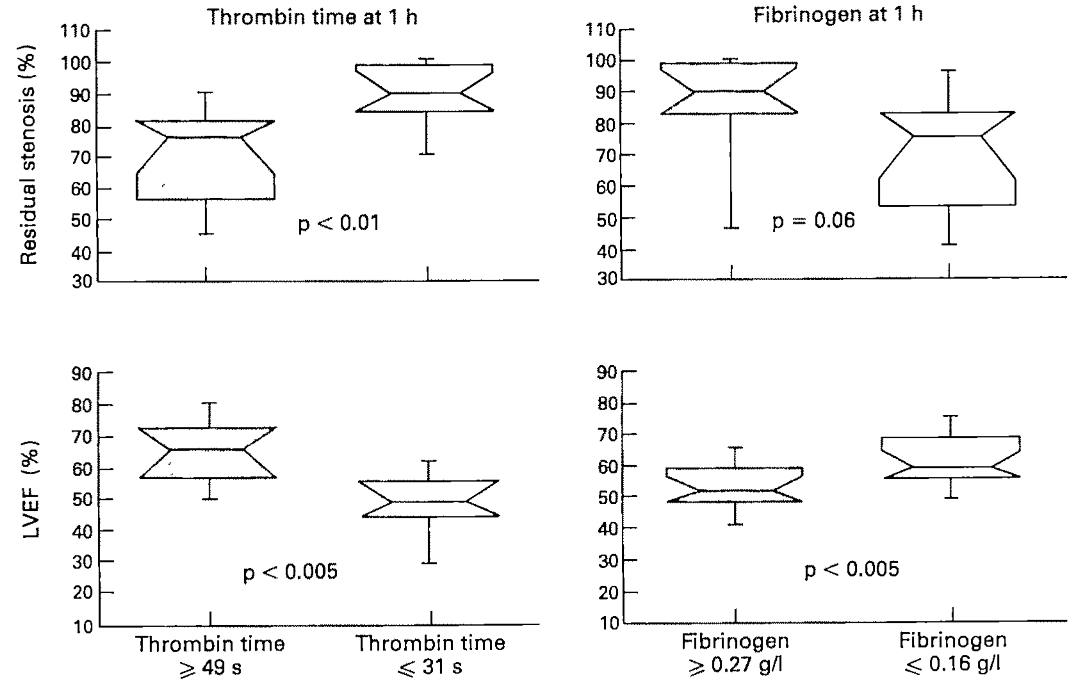

Figure 1 The effects of thrombin time and plasma fibrinogen one hour after streptokinase on residual coronary stenosis and left ventricular ejection fraction (LVEF). These data are for all of the 44 patients and compare the highest (n = 11) and lowest (n = 11) quartile ranges for each coagulation variable. Each box plot displays the 10th, 25th, 50th, 75th and 90th percentile values. Notches represent 95% confidence intervals about the median.

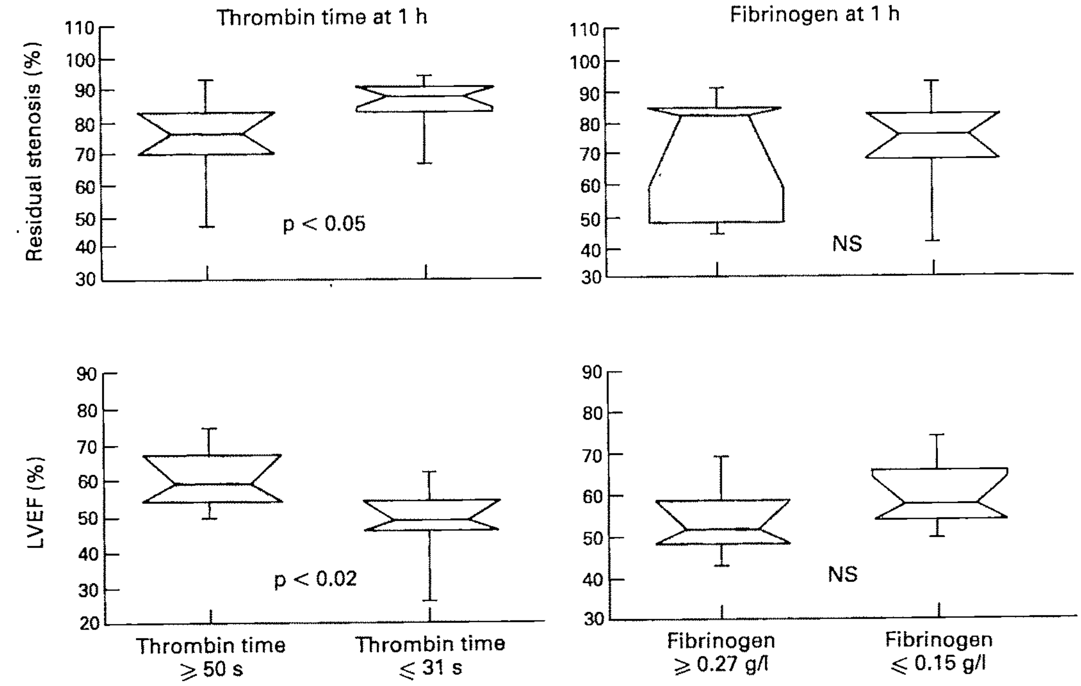

Figure 2 The effects of thrombin time and plasma fibrinogen one hour after streptokinase on residual coronary stenosis and left ventricular ejection fraction (LVEF). These data are for the 35 patients with patency of the infarct related artery and compare the highest (n = 9) and lowest (n = 9) quartile ranges for each coagulation variable. Each box plot displays the 10th, 25th, 50th, 75th and 90th percentile values. Notches represent 95% confidence intervals about the median.

Table 3 Relation between coagulation variables, residual coronary stenosis, and left ventricular ejection fraction

	Coagulation variable 1 hour after streptokinase			
	Thrombin time (s)		*Fibrinogen (g/l)*	
	*r**	*p Value*	*r**	*p Value*
All patients (n = 44):				
Residual stenosis (%)	−0·43	<0·005	0·28	0·07
LVEF (%)	0·38	<0·02	−0·29	0·05
Patients with patent IRCA (n = 35):				
Residual stenosis (%)	−0·38	<0·05	—	NS
LVEF (%)	0·32	0·06	—	NS

*Correlation coefficient (Spearman's rank method). IRCA, infarct related coronary artery.

Plasma fibrinogen concentrations one hour after streptokinase also correlated weakly with left ventricular ejection fraction when data for all patients were analysed. The interquartile group comparison confirmed that patients in the lowest range for fibrinogen concentration had significantly better preservation of ejection fraction (fig 1). When the analysis was confined to patients with a patent infarct related artery neither the correlation with ejection fraction nor the interquartile group comparison was significant.

Discussion

High plasma fibrinogen concentrations after thrombolytic therapy are often associated with non-patency of the infarct related coronary artery.[1 2] In our study, however, this association could not be tested because all the patients showed profound reductions in circulating fibrinogen that exceeded 80% in every case. Nevertheless, quantitative analysis of residual coronary stenosis showed that the degree of arterial patency correlated significantly with the level of defibrination when this was assessed by measurement of thrombin time. The importance of this correlation was emphasised by the interquartile group comparison which showed that a thrombin time of more than 49 seconds after streptokinase was associated with a median residual stenosis of 74%, compared with 90% for a thrombin time of less than 31 seconds. Part of this difference might be explained by non-patency of the infarct related artery in patients who did not defibrinate sufficiently in response to streptokinase. This does not, however, provide the full explanation because the difference, though more weakly significant, persisted even when patients with non-patency were excluded from analysis indicating that the association between high grade residual stenosis and attenuation of the thrombin time response was not merely the result of failed thrombolysis. The data suggest, therefore, that vigorous defibrination early after streptokinase, as indicated by significant prolongation of the thrombin time, ensures more effective thrombolysis and a more widely patent infarct related artery.

Arterial patency is a major goal of thrombolytic therapy that may have an important independent influence on long term prognosis.[4] The degree of arterial patency, however, as reflected by residual stenosis, has received less attention as a predictor of outcome although, in interventional studies, patients treated by direct angioplasty have been shown to have more widely patent arteries and better preservation of ventricular function than those treated by intracoronary streptokinase.[12] The findings in our study are to some extent analogous, in that an exaggerated thrombin time response was associated not only with a more widely patent coronary artery but also with better preservation of left ventricular ejection fraction. Although correlations between thrombin time and left ventricular ejection fraction were generally weak, and just failed to reach statistical significance, in the subgroup with coronary patency interquartile group comparison with data on thrombin time showed highly significant differences between residual ejection fractions for patients in the highest and lowest quartile ranges. Thus a thrombin time of more than 49 seconds was associated with a median ejection fraction of 65% compared with only 49% for a thrombin time of less than 31 seconds. Similar differences were shown when patients with non-patency of the infarct related artery were excluded from the analysis, again indicating that these findings were not merely a reflection of the known association between failed thrombolytic therapy and more extensive myocardial injury. Thus the data suggest that the level of defibrination, as shown by the thrombin time one hour after streptokinase infusion, may have an important influence on the residual left ventricular ejection fraction after acute myocardial infarction.

Although mechanisms relating defibrination to ejection fraction are not clear, the degree of arterial patency may play a contributory part. Thus vigorous defibrination produces a more widely patent infarct related artery that may permit more effective and perhaps earlier reperfusion leading to greater myocardial salvage. A less vigorous response, on the other hand, associated with high grade residual stenosis, is unlikely to restore adequate perfusion, particularly after thrombolytic therapy when the dynamics of coronary flow are adversely affected by plaque rupture and intraluminal thrombotic debris.[10] Nevertheless, residual stenosis and ejection fraction were not significantly correlated in our study indicating that other factors may also play a part in the association between defibrination and left ventricular function. Recent experimental data suggest that thrombolytic therapy may reduce infarct size independently of reperfusion and,[13 14] if the same applies clinically, defibrination may influence myocardial salvage directly; although whether this contributed to the findings in our study remains speculative.

Although the level of defibrination as measured by thrombin time correlated with residual stenosis and left ventricular ejection fraction, plasma fibrinogen itself correlated only weakly with these variables, and not at all when patients with non-patency of the infarct related artery were excluded from the analysis. This may reflect the relative inaccuracy of the

Clauss method,[8] which, although widely used for assessment of fibrinogen responses to thrombolytic therapy,[1-3] may give falsely low values if fibrin degradation products are present. Indeed, there has been some inconsistency about the value of fibrinogen assay by this method for assessing responses to thrombolytic therapy and at least one group of investigators has reported no relation with coronary patency.[3] It is perhaps not surprising, therefore, that when defibrination was measured by plasma fibrinogen, it failed to correlate with residual stenosis because this would demand of the assay a level of accuracy beyond that required for an all or none prediction of patency. Thrombin time, on the other hand, measures the functional integrity of circulating fibrinogen and is not affected by fibrin degradation products. Probably for this reason it provided a better test of the thrombolytic efficacy of streptokinase in our study.

It was our specific purpose to evaluate laboratory measurements of defibrination early after thrombolytic therapy for predicting coronary patency and left ventricular fraction at discharge from hospital when decisions about further management are usually made. Thus angiography was delayed from three to nine days when recovery from the acute phase of infarction was complete. Even at this fairly late stage, however, reversible myocardial stunning continues to make a variable contribution to alterations in ejection fraction.[15] Moreover, any time delay between treatment and angiography is associated with continued remodelling of the lesion within the infarct related artery, driven partly by the ongoing lytic effects of treatment, and partly by endogenous mechanisms.[10] Taken together these factors may have blunted the predictive value of our measurements by weakening correlations between defibrination and the angiographic data. Indeed, the fact that thrombin time one hour after streptokinase infusion remained significantly related to both residual stenosis and ejection fraction about a week later confirms the potential value of this test for monitoring responses to treatment.

The potential benefits of exaggerated defibrination must be set against the risk of bleeding, which affected two patients in our study. Fibrinogen degradation products have complex adverse effects on haemostasis,[16] and it is noteworthy that both patients with bleeding complications had high baseline fibrinogen concentrations that declined by 96% in response to streptokinase infusion. This may well have contributed towards their tendency to haemorrhage although in general the magnitude of systemic defibrination and its laboratory derangements have not been shown to correlate with bleeding.[17 18] Thus neither patient who bled had prolongation of the thrombin time beyond 40 seconds indicating that this particular measure of defibrination may not help identify patients at risk.

The findings in this study may have implications for clinical practice. Thus whereas some previous investigators have found that fibrinogen depletion encourages coronary patency after thrombolytic therapy[1 2] our study indicates that the more exaggerated the defibrination, the greater the coronary patency and the better the preservation of ventricular ejection fraction at the time of discharge from hospital. Simple measurement of thrombin time one hour after treatment seems particularly useful for assessing responses to treatment, values above 49 seconds being associated with the best angiographic results.

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Br Heart J 1992;68:176–80

Early and long term results of re-operation for coronary artery disease

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Abstract

***Objective*—To define the incidence, possible causes, operative procedure, and early and medium term results of patients undergoing reoperation for coronary artery disease.**

***Design*—A retrospective analysis of patients undergoing reoperation in one hospital during a 10 year period.**

***Setting*—A regional cardiothoracic centre.**

***Patients*—115 patients had reoperation for recurrent angina, 1–17 years (mean (SD) 7·4 (3·9)) after primary revascularisation.**

***Main outcome measures*—They received 279 grafts (2·4 grafts per patient); 58% of the grafts were anasatomosed to previously grafted vessels. The internal mammary artery was used in 87% of patients who required grafts to the left anterior descending coronary artery.**

***Results*—Reoperation accounted for 8·3% of the total number of patients who underwent coronary bypass grafting. Graft failure alone or in combination with other factors was judged to be the cause of recurrence of symptoms in 87%. 42% of patients had two or more coronary risk factors. The early mortality was 5·2% and the actuarial survival at five and 10 years was 90·4% and 88·4% respectively. 85% of the survivors had initial complete relief of angina and 14% had partial improvement. Freedom from recurrent symptoms at five and 10 years was 66·6% and 34·6% respectively.**

***Conclusions*—Vein graft failure either alone or in combination with progression of native coronary disease is the main cause for symptomatic deterioration after bypass grafting. Reoperation can be performed with slightly increased risk and can give good early and medium term results.**

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Despite the encouraging impact of coronary artery bypass grafting on the natural history of ischaemic heart disease, the procedure remains a palliative one. Recurrence of angina occurs in 3·5%–4·5% of patients each year after coronary artery bypass grafting (CABG).[1] The incidence of reoperation is increasing because of the progressive nature of the disease.[2] It is reported that reoperation could carry a higher morbidity and mortality[3 4] with a variable chance of symptomatic improvement.[5-8] The aims were to analyse our experience with reoperation in an attempt to define the possible factors causing recurrence of angina after the original operation, and to characterise the early and long term results of reoperation.

Patients and methods

Between January 1981 and December 1990 a total of 115 patients had reoperations for recurrence of their symptoms after primary CABG. These patients represent 8·3% of the total number who underwent coronary operations during this period. Fourteen patients in this group had had their first operation in other hospitals, and were referred to Harefield Hospital for their reoperation. There were 109 men and six women with an age range of 36–71 (mean 53·7 (7·6)) years. Figure 1 shows that the time interval between the two operations ranged from one to 17 (mean 7·4 (3·9)) years. Seventy one percent of patients had their second operation five years or more after the first. According to the Canadian Heart Association Classification of Angina, nine patients were in class II, 66 in class III, and 40 in class IV (fig 2). Table 1 shows the incidence of different risk factors amongst the patients. Forty two percent of patients had two or more of the listed risk factors.

ANGIOGRAPHIC FINDINGS

A total of 294 grafts were inserted in the first

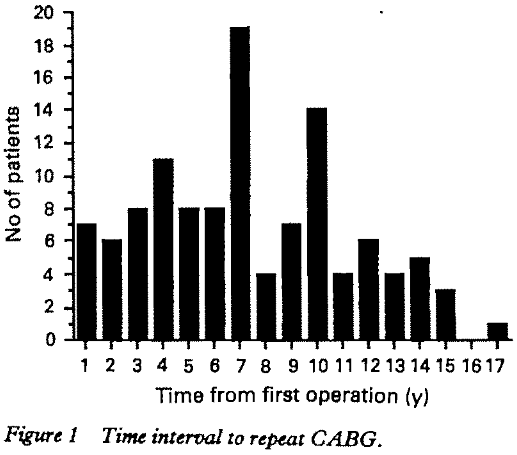


Figure 1 Time interval to repeat CABG.

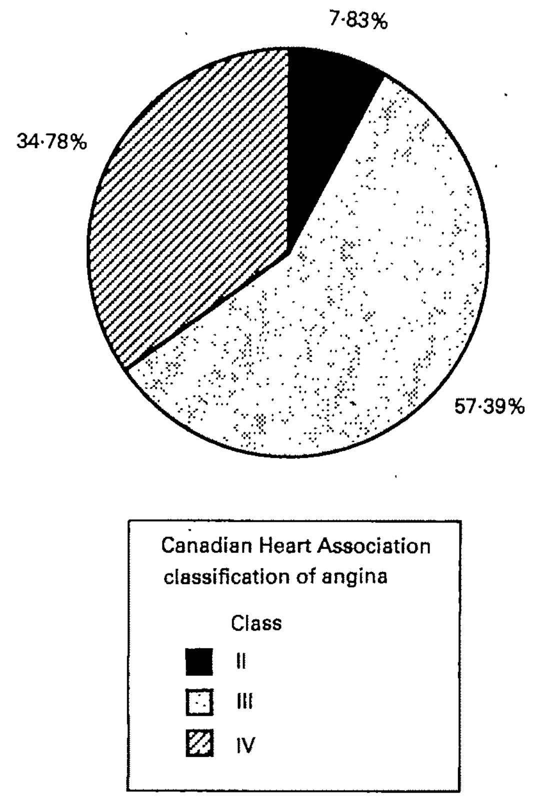


Figure 2 The severity of angina in patients presenting for repeat CABG.

Table 1 Preoperative risk factors

	Patients (n)	*% of total group*
Family history	48	41·7
Previous MI	35	30·4
Smoking	30	26·1
Hyperlipidaemia	21	18·3
Hypertension	17	14·8
Obesity	7	6·1
Diabetes mellitus	4	3·5

MI, myocardial infarction.

operation with a mean of 2·6 grafts in each patient. Of these, the long saphenous vein was used in 288 instances, and the internal mammary artery (IMA) in six patients.

The angiographic study before reoperation showed that 229 grafts were occluded or severely diseased (77·9%) and 65 were patent (22·1%). Five out of the six IMAs used at the first operation were still patent at reoperation. Figure 3 shows the incidence of occlusion of different grafts. The possible causes of deterioration of symptoms were assessed angiographically and table 2 lists these. Graft failure was the sole reason in 46·1%, and in association with progression of native disease or incomplete revascularisation or both, graft failure was implicated in a further 42·5% (total of 88·6%) of cases. Left ventricular function was assessed as good (ejection fraction (EF) >60%) in 75%, mildly impaired (EF 40%–60%) in 16%, and poor (EF <40%) in 9% of patients.

Table 2 Causes of recurrent angina

	Patients (n)	*% of total group*
Graft failure	53	46·1
Progression of underlying disease	13	11·4
Incomplete revascularisation	2	1·7
Progression and graft failure	37	32·2
Graft failure and incomplete revascularisation	5	4·3
Graft failure, progression and incomplete revascularisation	5	4·3

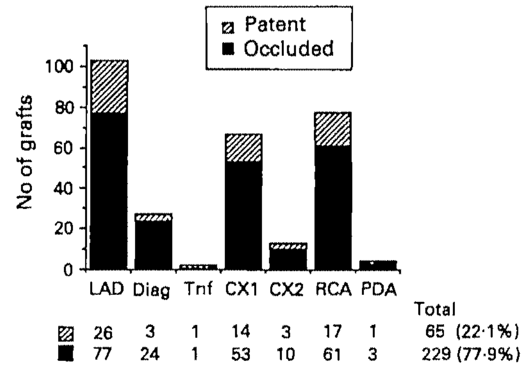


Figure 3 Angiographic findings before reoperation. LAD, left anterior descending coronary artery; Diag, diagonal branch; Trif, tri-furcation; CX1, circumflex branch 1; CX2, circumflex branch 2; RCA, right coronary artery; PDA, posterior descending coronary artery.

OPERATION DATA

One IMA previously anastomosed to the left anterior descending coronary artery (LAD) was damaged during dissection, being adherent to the undersurface of the sternum. Intermittent aortic cross clamping and core cooling to 30°C was used in 88 patients (76·5%), and cardioplegia with St Thomas's solution in 27 patients (23·5%). During reoperation 279 grafts were inserted with a mean of 2·4 grafts per patient. Eighteen patients had single grafts, 42 had double grafts, 43 had triple grafts, and 12 had quadruple grafts. At reoperation 51 patients had grafts only to previously grafted vessels (44·3%), 51 had regrafts as well as grafts to vessels not grafted before, and only 13 patients (11·4%) had grafts to vessels not grafted at the first operation. Figure 4 shows the site and pattern of grafting. Fifty eight percent of the grafts were inserted to vessels previously grafted because of total occlusion or extensive graft atherosclerosis. Forty two percent of the grafted vessels were not grafted before and showed evidence of progression of native vessel disease. The LAD was grafted in 83 patients. Ninety two percent of them had been previously grafted, whereas 8% had not. Out of the 83 patients, 70 had single IMA and two had double IMA grafts.

Fourteen patients had twenty endarterectomies at reoperation and two had the aortic valve replaced with aortic homografts. All patients were prescribed aspirin and dipyridamole in the postoperative period.

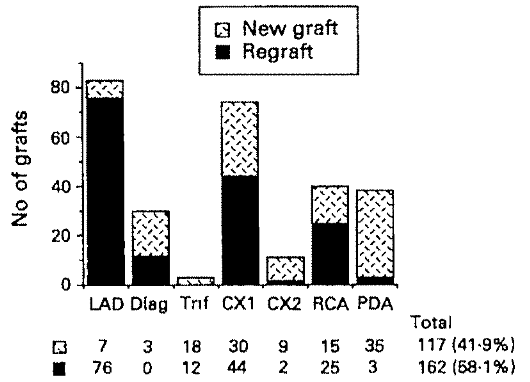


Figure 4 Sites and pattern of grafting at reoperation. Abbreviations as in fig 3.

Table 3 Risk factors and mortality

Patient	*Cause of death*	*Risk factors*
1	CVA	Smoking, obesity, family history
2	CVA	Hypercholesterolaemia, hypertension, obesity, impaired left ventricular function, family history
3	LCOP	Previous myocardial infarction, hypertension, impaired left ventricular function, family history
4	LCOP	Previous myocardial infarction, impaired left ventricular function, smoking
5	CVA	Previous myocardial infarction, impaired left ventricular function, smoking
6	LCOP	Previous myocardial infarction, smoking

CVA, Cerebrovascular accident; LCOP, Low cardiac output.

Mortality and morbidity

Six early deaths occurred within 30 days of reoperation (5·2%). The cause of death was low cardiac output in three and cerebrovascular accident in three. In all of the early deaths, at least two risk factors were present (table 3). Four of the early deaths had poor left ventricular function before operation. Table 4 shows the postoperative complications. The actuarial survival rate at five and 10 years was 90·4% and 88·4% respectively (fig 5).

RELIEF OF SYMPTOMS AND LATE OUTCOME

Complete relief of symptoms was achieved in 93 patients (85·3%) for at least one year. Fifteen patients (13·8%) had incomplete relief of their angina and one patient (0·9%) had no improvement. Those who had initial disappearance of angina remained free of symptoms for a mean period of 42 (22) months. Freedom from recurrence of angina at five and 10 years was 66·6% and 34·6% respectively (fig 6). After a follow up period between one and 10 years (mean 64 (32) months), 43 patients had no symptoms, forty three had class I or II angina, and 14 patients had class III or IV angina. Five patients underwent a third operation without deaths. Early postoperative angiography was performed for 47 patients within the first year after reoperation. This was done as a routine postoperative assessment in 43 patients and to assess residual symptoms in four patients. Out of 121 grafts examined 85·7% were patent (fig 7).

Discussion

The need for reoperation after primary myocardial revascularisation is increasing. This is probably due to the increasing number of CABG operations, the progressive nature of the disease, and the development of accelerated disease in the vein grafts in the absence of effective methods of prevention. Previous studies have shown that the occlusion rate of saphenous vein grafts is around 12%–20% during the first year, and 2%–4% annually for four to five years with subsequent doubling of the rate.[9] It is estimated that 1·8%[10] to 5·5%[11] of CABG operations are reoperations. In our study, 8·3% of the total number of CABGs were reoperations during this period. This incidence is higher than average, possibly due to the fact that Harefield Hospital tends to act as a tertiary referral centre.

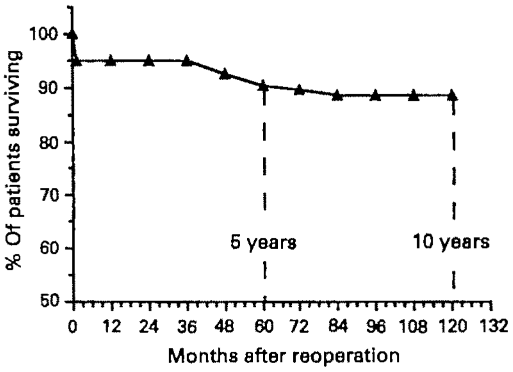


Figure 5 Actuarial survival of patients after reoperation (n = 115).

The time interval between the two operations ranged from 1–17 (mean 7·4 (3·9) years). Seventy three percent of patients required their reoperation five years or more after the first. A recent report has found that the time to reoperation is becoming longer, as a result of decreased early graft occlusion.[12] This may be a reflection of improving technique with the recognition of the importance of minimising the damage to the vein during harvesting.[13] The possible causes of recurrent angina seem to be changing. In our study, graft failure was the sole reason in 46·1% of cases; there was an association with other causes in 42·5% (total 88·6%). Progression of native vessel disease alone or combined with other causes was found in 49·9% of our patients. Early reports,[14] showed incomplete revascularisation to be implicated in a high percentage of cases. Our findings are comparable with more recent reports.[3 15] The number of grafts per patient increases with surgical experience.[16] In this series, 279 grafts were inserted with a mean of 2·4 grafts for each patient. Janardhan *et al*[5] has

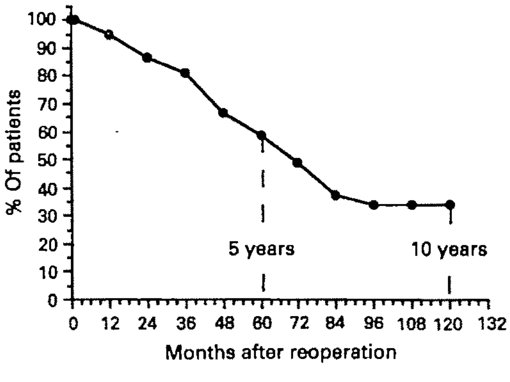
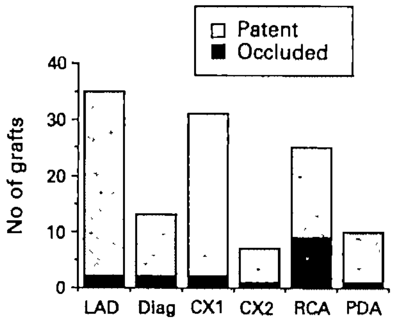


Figure 6 Freedom from recurrence of symptoms after reoperation (n = 115).

Table 4 Perioperative morbidity

	Patients (n)	*% of total group*
Bleeding	3	2·9
Perioperative myocardial infarction	4	3·8
Cerebrovascular accident	4	3·8
Arrhythmia	14	12·2
Complete heart block	1	
Left bundle branch block	1	
Right bundle branch block	2	
Atrial fibrillation	9	
Supraventricular tachycardia	1	

Figure 7 Graft patency of 121 grafts at one year after reoperation. Abbreviations as in fig 3.



	LAD	Diag	CX1	CX2	RCA	PDA	Total
□	33	11	29	6	16	9	104 (86·0%)
■	2	2	2	1	9	1	17 (14·0%)

recently reported 2·5 grafts for each patient. Most of our grafts to the LAD (91·6%), were inserted into previously grafted vessels. This is attributed to the low use of the IMA in the first operations in this cohort of patients. It was found also by Pidgeon *et al*,[15] that 77% of LAD grafts at reoperation were to previously grafted vessels. The lack of use of the IMA to LAD was found to be one of the predictors of reoperation by Cosgrove *et al.*[16] The superiority of the IMA over saphenous vein grafts is well documented and is due to several factors including endothelial production of large concentrations of endothelium dependent relaxing factor (EDRF) by arterial grafts.[17 18] The IMA was used in 87% of patients who required graft to the LAD in our series of reoperations.

Hospital mortality in our series was 5·2%, which is comparable with previous reports.[3 4 19] Four out of the six early deaths occurred in patients with impaired left ventricular function. The increased risk of reoperation is explained by advancing age, progression of vascular disease, and deterioration of ventricular function.[3] The incidence of perioperative myocardial infarction in our patients was 3·8%. It was reported by others to be around 7·1%.[3 14] The higher incidence of perioperative myocardial infarction may be due to embolisation from previous grafts at the time of manipulation of the heart or the graft. Therefore we advocate in agreement with other authors that the grafts to be replaced should be tied off before any cardiac manipulation.[20]

Angina was completely relieved for at least one year in 85% of our patients. This group remained symptom free for a mean period of 42 (22) months. Partial improvement was noted in 14% of patients, but 1% had no change in symptoms. Although some previous reports,[6–8] have documented less favourable results, more recently, Lytle *et al*, reported that 50% of patients were symptom free five years after the second operation.[3]

Vein graft atherosclerosis was shown in this study and in other reports,[3 14] to be the main reason for recurrent angina after CABG. Many pathophysiological studies implicate platelets[21 22] and lipids[23–25] as possible mediating factors in the development of atherosclerotic lesions. There has been evidence that antiplatelet treatment has an effect in improving graft patency after CABG.[26–28] Cholesterol lowering treatment has been shown recently to induce regression of disease in native vessels as well as bypass grafts.[29 30]

To enhance the benefit of primary myocardial revascularisation, it has been our policy to use at least one IMA routinely, follow a meticulous technique during harvesting of the vessel, prescribe antiplatelet treatment postoperatively, and achieve strict control of hyperlipoproteinaemias.

In conclusion, reoperation for recurrent angina can be performed with slightly increased risk, and can achieve good symptomatic relief for a period of up to 10 years. The main causes of deterioration in symptoms after the first operation are failure of the vein graft followed by progression of native vessel coronary disease. This study highlights the need for developing methods for effectively preventing such problems in these patients.

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ABSTRACTS IN CARDIOLOGY

Spasm and sudden death

Sudden deaths in which necropsy shows a structurally normal heart and no cause of death are a rare phenomenon but cause great distress to relatives who are trying to understand the event. Some insight into the cause of this phenomenon can be gained by investigating patients who have been resuscitated from out-of-hospital ventricular fibrillation (VF). The paper by Myerburg *et al* reports that coronary artery spasm in subjects without obstructive atherosclerotic disease can precipitate VF. This condition could not be recognised by any pathological feature at necropsy but could be suspected if anginal type chest pain had been reported during life. Having said this, coronary spasm cannot be said to be common, occurring in no more than 1·4% of subjects who present with out-of-hospital VF. The further question of whether spasm can precipitate VF in subjects who have co-existent obstructive coronary disease remains to be answered.

MJ DAVIES

Life-threatening ventricular arrhythmias in patients with silent myocardial ischaemia due to coronary artery spasm

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Abstract

Background.—Silent myocardial ischaemia in patients with coronary atherosclerosis is associated with an increased risk of adverse cardiac events, including sudden death. The relation between silent ischaemia and the initiation of potentially fatal ventricular arrhythmias has not been defined, however.

Methods.—As part of a long-term study of sudden cardiac death, data on arrhythmias, coronary anatomy, and responses to ergonovine testing to provoke coronary artery spasm were collected prospectively among survivors of out-of-hospital cardiac arrest who had no flow-limiting coronary artery lesions, prior myocardial infarctions, or other structural causes of cardiac arrest and no angina pectoris. Associations between silent myocardial ischaemia due to coronary artery spasm and the occurrence and characteristics of life-threatening ventricular arrhythmias were studied by both invasive and noninvasive techniques.

Results.—Silent ischaemic events were associated with the initiation of life-threatening ventricular arrhythmias in five patients with induced or spontaneous focal coronary artery spasm (or both). These patients were identified among a group of 356 survivors of out-of-hospital cardiac arrest who were evaluated between 1980 and 1991. In two of the five patients reperfusion, rather than ischaemia itself, correlated with the onset of the ventricular arrhythmia. Only one of the five had an inducible arrhythmia during electrophysiologic testing. Titration of the dose of a calcium-entry-blocking agent (verapamil, diltiazem, or nifedipine) against the ability of ergonovine to provoke spasm was successful in preventing both the provocation of spasm and arrhythmias in all four patients who were tested.

Conclusions.—Silent myocardial ischaemia due to coronary artery spasm can initiate potentially fatal arrhythmias in patients without flow-limiting structural coronary artery lesions. The role of silent ischaemia, reperfusion, or both in the initiation of fatal arrhythmias in larger groups of patients with advanced coronary artery lesions remains to be defined. (*N Engl J Med* 1992;326:1451–5.)

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Influence of power and aerobic exercise training on haemostatic factors after coronary artery surgery

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Abstract

***Objectives*—To determine the effects of aerobic and power exercise training on haemostatic factors after coronary artery surgery and to compare the effect of the two exercise programmes.**

***Design*—A prospective randomised controlled study of six months aerobic and power exercise training in men after coronary artery surgery.**

***Setting*—Exercise rehabilitation classes in a teaching hospital in Glasgow.**

***Patients*—55 men within 12 months of coronary artery surgery recruited from surgical centres and medical clinics and asked to participate in the study.**

***Interventions*—Assessments, including a treadmill test, measurements of haemoglobin, platelet, fibrinogen, factor VIIc, and fibrinopeptide A concentrations, and packed cell volume, done at baseline, three months, and six months. Patients in the two exercise groups attended training sessions three times weekly for six months. Control patients had no formal exercise training but continued with their leisure time activities.**

***Main outcome measures*—Exercise performance on a treadmill, haematology, and haemostatic factor assays at baseline, three months, and six months.**

***Results*—In the aerobic trained group exercise performance increased significantly over baseline at three months (interval change 146·7, 95% confidence interval (95% CI) 52·5 to 240·9 s, p = 0·003) and was maintained at six months (interval change 172·1, 95% CI 63·3 to 280·9 s, p = 0·002). In the power trained groups significant improvement in exercise performance was delayed until six months (interval change 99·9 s, 95% CI 20·3 to 170·5 s, p = 0·01). Exercise performance in the control did not change significantly. Haemoglobin, concentration, packed cell volume, and platelet counts did not change significantly at any time. Fibrinogen concentration was significantly lower in the aerobic group than the other two groups at three months (2·96 g/dl compared with 3·3 g/dl and 3·87 g/dl in the power and control groups, p = 0·01). The power group had a lower fibrinogen concentration than the control group (p = 0·04). The lower fibrinogen concentration in the aerobic group was maintained at six months. There was a gradual rise in factor VIIc concentrations in the aerobic and control groups compared with a small fall in the power group. Fibrinopeptide A concentrations showed no consistent changes.**

***Conclusions*—Aerobic exercise training after coronary artery surgery causes an early favourable change in treadmill performance and in fibrinogen concentrations, that is maintained with further training. Power exercise training causes delayed benefit in treadmill performance. It also causes a small fall in fibrinogen concentrations. These changes may be relevant in reducing cardiovascular morbidity from graft failure and occurrence of myocardial infarction after coronary artery surgery.**

(*Br Heart J* 1992;68:181–6)

Fibrinogen and factor VII are independent risk factors for coronary artery disease and myocardial infarction.[1,2] High fibrinopeptide A concentrations are found in patients with unstable angina and acute myocardial infarction.[3–5] The effects of acute exercise on haemostasis have been studied in normal people and in patients with coronary artery disease, with varying results. These are enhanced fibrinolysis,[6,7] increased platelet count and aggregation[6,8] and potentiation of coagulation by increased concentrations of factor VIII.[7,9,10]

By contrast with acute exercise, little attention has been paid to the effects of chronic exercise on coagulation factors.[6,11]

Coronary artery surgery relieves angina and in selected subgroups of patients, prolongs life but it has had no impact on subsequent myocardial infarction.[12–14] Also graft failure remains problematical and can be caused by thrombosis and progressive atherosclerosis,[15] both of which are influenced by haemostatic factors. Exercise training has been found to improve exercise capacity[16–18] and quality of life[19,20] in patients after coronary artery surgery. Exercise reduces cardiovascular risk through mechanisms that are as yet unclear. Intense aerobic exercise has been shown to reduce total cholesterol concentration and to increase high density lipoprotein (HDL) concentrations[21,22] and exercise training after myocardial infarction has resulted in favourable lipoprotein changes.[23]

It is possible that exercise training can increase the benefits of coronary artery surgery by effecting changes in cardiovascular risk factors that are not influenced directly by myocardial revascularisation. Such risk factors would include lipoproteins, fibrinogen, and factor VIIc concentrations. Exercise training as widely used in cardiac rehabilitation is usually aerobic exercise using low resistance high repetition exercises involving the rhythmic movement of large muscle groups. Power exercise has been little studied in cardiac patients because of fears associated with isometric exercise (high intensity low repetition exercise such as weight lifting) and its deleterious effects on blood pressure and therefore afterload. Power exercise is not, however, strictly isometric in that it also involved repetitious movements of a moderate weight load, by large muscle groups, with consequent increases in peripheral blood flow, cardiac output, ventilation, and oxygen consumption. In published reports it has been used only in previously trained patients.[24,25]

There are few studies on exercise training in patients after coronary artery surgery alone. In most reports, such patients form part of a group of "cardiac patients" including those with angina and previous myocardial infarction. It has been reported, however, that patients after coronary artery surgery achieved as much functional improvement as the other cardiac patients studied simultaneously.[18,26] Age and extent of revascularisation do not appear to influence exercise tolerance.[27] Those who dropped out of rehabilitation had worse outcomes in terms of return to work, smoking, and hospital.[28] In the PERFEXT study patients after coronary artery surgery accounted for a third of the group. The exercise trained patients showed similar haemodynamic benefits such as increased Vo_2 max to those with other forms of coronary artery disease.[29,30] Exercise training has been shown to cause beneficial changes in lipoprotein concentrations after coronary artery surgery.[31]

The haemostatic system is assuming a prominent role in pathogenesis and progression of coronary artery disease. Fibrinogen concentrations are high among patients with coronary artery disease and smokers.[1,2] Low factor VIIc concentrations are thought to protect against thrombotic events as high factor VII activity causes raised thrombin production.[32] Fibrinopeptide A is a major breakdown product of thrombin and its concentrations reflect activity of the coagulation system.

We studied the effects of six months supervised graduated aerobic and power exercise training on exercise capacity, haematological, and haemostatic factors in 55 men within 12 months of coronary artery surgery. This was part of a larger study of exercise rehabilitation after coronary artery surgery.

Patients and methods

Fifty five men (mean age 58, range 32–70) within 12 months of coronary artery surgery (range six weeks to 12 months) were studied. Table 1 shows patients' characteristics at baseline. No significant differences were found between the groups. Assessments done at baseline, three months, and six months included a treadmill exercise test with modified Balke II protocol, body weight, skin fold thickness (biceps, triceps, scapular, and abdominal), haemoglobin, platelet, factor VIIc, fibrinogen, and fibrinopeptide A concentrations, and packed cell volume. Patients were recruited from a surgical centre and medical clinics and asked to participate in the study. Those unable to exercise on a treadmill or to attend exercise classes were excluded. After baseline assessment, patients were randomised to three groups: (1) control (no formal exercise training); (2) six months graduated supervised aerobic exercise training; (3) six months graduated supervised power exercise training. Informed consent was given by each patient and the study was approved by the local ethics committee.

Table 1 Patient characteristics at baseline

	Control	*Aerobic*	*Power*
No	20	15	20
Age (y) mean (SD)	56 (7)	57 (9)	60 (6)
No grafts (mean)	3·1	2·8	3·4
Drugs:			
Aspirin	18	12	17
Dipyridamole	17	11	15
Anti-ischaemia	4	0	1
Diuretic	4	1	4
ACE I	0	1	0
Previous MI	8	7	12
Current smokers	2	2	1
Previous smokers	10	7	14
Employed	7	4	7
Off work	5	4	4
Retired	8	6	9
Time since surgery (wk) median (range)	12 (8–28)	12 (6–36)	12 (6–44)

EXERCISE CLASSES

Patients in both exercise groups attended exercise training sessions three times weekly in the same place supervised by a physiotherapist and a rehabilitation sister or a doctor. Each patient's session lasted from 12 to 60 minutes.

Aerobic exercises performed were modified from the Canadian Airforce PBX training programme. These were running on the spot, step ups, arm circling, star jumps, standing trunk curls, bridging, trunk rotation, side lying with hip abduction, arm raising, trunk side flexion, and crook lying with trunk rotation. The work performed was serially increased by increasing the number of repetitions of the exercises performed. Power exercises were based on weight training and Universal Multigym apparatus in which moderate weight loads are connected through a pulley system. Exercises performed were leg extensions, hamstrings curl, biceps curl, push down, pull down, press behind neck, bench press, pulley row, military press, and sit ups. The work performed was serially increased for each individual by increasing the weights and number of repetitions of each movement. There were rest periods of 45 s between each station. At the end of the training period each patient was exercising to his maximum. No heart rate or other cardiovascular monitoring was done during the exercises. Judgements regarding progression to the next stage of the programme were based on patient's performance and symptoms. Each patient ended the session with a ride on a stationary bicycle. Attendance records were kept.

TREADMILL TESTS

These were performed with a Marquette Case II system with modified Balke II protocol. This protocol consists of three minute stages. The speed and gradient are increased after the first stage from 3·2 km/h gradient 0% to 4·8 km/h gradient 4%. The speed then stays constant while the gradient increases by 4% per stage until the 7th stage when the speed increases to 7·2 km/h gradient 20%.

Two initial exercise tests were performed and the average of these was taken as the baseline exercise performance. Patients were familiar with the equipment, most of them having had exercise tests before their operation as part of their work up. We therefore considered that the treadmill test was a fair means of assessing exercise capacity in this group of patients. The exercise tests were symptom limited unless ventricular arrhythmias, or significant hypotension occurred. All treadmill tests were performed in the morning.

BLOOD SAMPLES

Samples of blood were taken through an indwelling cannula after an overnight fast. There had been no exercise training in the preceding 18 hours. The first 30 ml was used for lipoprotein analysis; 5 ml was used for measurement of haemoglobin, packed cell volume and platelets, 5 ml for fibrinogen and factor VIIc concentrations, and 5 ml for fibrinopeptide A assay.

SAMPLE ANALYSES

The technicians performing the assays were unaware of the patients' group. Samples were stored at −85°C in plastic containers and tested in batches. Blood for factor VIIc and fibrinogen assays were stored for up to two weeks and fibrinopeptide A for up to six weeks. Haemoglobin concentration, packed cell volume, and platelet counts were measured automatically by Coulter counter.

FACTOR VIIc ASSAY

Factor VIIc was measured by the amount of correction of the one stage prothombin time found when patient's plasma is added to factor VII deficient plasma. The reagents required are available commercially and include factor VII deficient plasma, saline extract of brain, Owren's buffer, pH 7·35, calcium chloride 0·025 mol/l, patient's citrated platelet poor plasma and reference plasma containing 100 IU/dl of factor VII. After preparing serial dilutions of the reference plasma in Owren's buffer, 0·1 ml of factor VII deficient substrate plasma, 0·1 ml normal plasma dilution and 0·1 ml of saline extract of brain were placed into a glass test tube in a water bath at 37°C. The mixture was incubated for 30 s and 0·1 ml of calcium chloride (0·025 mol/l) is added. The clotting time was recorded. Each dilution was tested twice and the average clotting time was plotted on double log graph paper against calculated plasma factor VII concentration. The one in 10 dilution of normal plasma was considered to contain one unit of factor VII activity per ml (100 IU/dl). The patient's plasma was similarly assayed, with dilutions tested depending on the expected factor VII concentrations. The clotting time of the dilution of patient's plasma was converted to factor VII activity by extrapolation from the standard graph. The normal range is 60–150 IU/dl.

FIBRINOGEN ASSAY

The fibrinogen assay was carried out with a Multifibren kit (Behring) by a modification of the Clauss method. Multifibren consists of lyophilised α-thrombin from bovine plasma. The principle is that citrated plasma is clotted by the addition of a relatively large amount of thrombin; clotting time depends mainly on the fibrinogen content of the blood sample. Plasma was diluted one in nine with barbital buffer solution (pH 7·6) and the assay performed within 15 minutes: 0·2 ml of citrated plasma solution and 0·2 ml fibrintime were placed in a prewarmed test tube at 37°C, incubated for 60 s, and 0·2 ml of Multifibren was added. The clotting time was recorded. The result was converted to g/dl from a standard table of values supplied in the kit. Reference curves were checked with supplied control plasma (lyophilised human plasma). The normal range is 1·8–3·5 g/dl.

STATISTICAL ANALYSES

Results were considered on an intention to treat basis. All variables were analysed by analysis of variance and paired t test for normal data, Wilcoxon signed rank test for non-normal data within groups, and unpaired t test or Mann-Whitney U test for differences between the groups. Results are expressed as mean (SEM or 95% CI). Where the data were non-normal, non-parametric methods for calculating confidence intervals were used.

Results

There were no exercise related deaths or cardiovascular events. Patients in the exercise groups attended 55%–65% of the sessions. Two patients dropped out of the power training group after a few weeks due to problems with their surgical scars.

Treadmill time and workload was significantly improved in the aerobic exercise trained groups at three months and the improvement was maintained at six months, whereas in the power group significant improvement in treadmill performance was delayed until six months. The control group did not show any significant change in treadmill performance (tables 2 and

Table 2 Treadmill times at each assessment (s) mean (SEM)

	Baseline	*3 months*	*6 months*
Control	699·2 (80·9)	725·8 (82·3)	729·7 (78·8)
Aerobic	719·2 (79·2)	865·9 (72·8)	891·4 (74·4)
Power	800·4 (65·0)	852·0 (69·0)	900·3 (67·3)

Table 3 Interval change from baseline in treadmill times within the groups (s) mean (95% CI)

	3 months	6 months
Control	26·6 (−10·8 to 64·0)	30·6 (−34·9 to 96·1)
Aerobic	146·7 (52·5 to 240·9)	172·1 (63·3 to 280·9)
Power	51·6 (−29·0 to 132·2)	99·9 (20·3 to 179·5)

See text for p values.

Table 5 Factor VIIc concentrations (IU/dl) at each assessment (mean (SEM))

	Baseline	3 months	6 months
Control	101·22 (4·31)	107·95 (4·5)	109·6 (4·8)
Aerobic	100·4 (6 73)	108·2 (6·65)	113·67 (5·62)
Power	105·8 (4·24)	107 (4·45)	104·4 (3·39)*

*Power *v* aerobic p = 0·008 and power *v* control p = 0·06.

3). At three months, the interval change in performance between aerobic and power groups tended towards significance (p = 0·06), that between aerobic and control was significant (p = 0·005), and that between control and power was not (p = 0·28). At six months, the levels of significance for between group differences in performance were: aerobic *v* control p = 0·01, power *v* control p = 0·08, and aerobic *v* power p = 0·14. Haemoglobin, packed cell volume, platelet, or fibrinopeptide A concentrations, body weight, or mean skin fold thickness did not change significantly within or between groups at any time. Tables 4 and 5 show fibrinogen and factor VIIc concentrations. A significant fall in fibrinogen concentrations found in the aerobic trained group at three months (p = 0·01) was maintained at six months (p = 0·04) so that compared with the other two groups aerobic training had a favourable change in fibrinogen concentrations. (12% reduction after six months; compared to 2% reduction in the power group and 4% reduction in the control group). The median value for interval change in fibrinogen concentrations in the control group at three months is 0·1 g/dl.

At six months, there was a fall in the fibrinogen concentration in the power and control groups to values lower than at baseline but the difference was not significant. Values for interval change in fibrinogen concentrations between the groups were: at three months aerobic *v* control p = 0·0004, control *v* power p = 0·07, aerobic *v* power p = 0·0002, at six months aerobic *v* control p = 0·02, control *v* power p = 0·09, aerobic *v* power p = 0·05. Factor VII concentrations rose with exercise training in the aerobic group but fell slightly in the power trained group so that at the end of six months the difference between the groups was statistically significant (power *v* aerobic p = 0·008, power *v* control p = 0·06).

Discussion

The rationale for this study was to investigate the ways in which exercise training may increase the benefits of coronary artery surgery. We compared aerobic exercise training with power exercise training in part to allay fears about power exercise training in cardiac patients and to directly compare the two types of exercise training in previously untrained patients after coronary artery surgery.

Fibrinogen and factor VII are independent risk factors for atherosclerosis and thrombosis.[1] Exercise has been shown to protect against coronary artery disease both in primary[33–35] and secondary prevention studies,[36–38] although the mechanisms through which it exerts this influence are not clear. It does cause beneficial changes in lipoprotein profiles.[21–23]

Our preliminary results suggest a further mechanism by which chronic exercise is beneficial, specifically in men, after coronary artery surgery.

The study is one of effects and not mechanisms. A mechanism that has been suggested for the effects of exercise on haemostatic factors is that it reduces tissue hypoxia and lactic acid production after exercise due to improved cardiovascular performance with a reduced tendency to haemostasis. The tendency to increased membrane permeability and damage to muscle cells may also be reduced by exercise training[6] with a reduction in the activation of coagulation.

Several studies have been carried out on the effects of acute and chronic exercise on the fibrinolytic system but only limited studies on the effects of chronic exercise on haemostatic factors. Williams *et al* showed that physical conditioning by 10 weeks of training on a treadmill augments the fibrinolytic response to thrombotic stimuli such as venous occlusion.[39] Regular vigorous sporting activities enhance blood fibrinolysis by reducing blood plasminogen activator inhibitor capacity in healthy men, but do not affect this significantly in patients after myocardial infarction in a rehabilitation class.[40] This is by contrast with the findings of Estelles *et al* who showed that in patients after myocardial infarction in an exercise rehabilitation class, there was a slight improvement in fibrinolytic activity measured by plasminogen activator inhibitor activity compared with controls.[41] Drygas reported on

Table 4 Fibrinogen concentrations at each assessment and changes from baseline within the groups (g/dl)

	Fibrinogen concentrations at assessments (mean (SEM))			*Interval changes from baseline (mean (95% CI))*	
	Baseline	*3 months*	*6 months*	*3 months*	*6 months*
Control	3·48 (0·22)	3·87 (0·30)	3·34 (0·19)	0·36 (−0·18, 0·56)	−0·15 (−0·42, 0·12)
Aerobic	3·40 (0·21)	2·96 (0·16)*	2·98 (0·16)†	−0·43 (−0·63, −0·23)‡	−0·41 (−0·7, −0·12)§
Power	3·18 (0·12)	3·33 (0·13)	3·12 (0·12)	0·15 (−0·05, 0·35)	−0·06 (−0·26, 0·14)

*Aerobic *v* control p = 0·01 and aerobic *v* power p = 0·04.
†Aerobic *v* control p = 0·02 and aerobic *v* power p = 0·08; ‡p = 0·01; §p = 0·04.

changes in blood platelet function, coagulation, and fibrinolytic activity in response to varying degrees of acute exercise in 47 healthy men. He found that static exercise of short duration did not cause changes. Prolonged aerobic exercise consisting of 60 minutes on a bicycle ergometer caused strong activation of the fibrinolytic system and a slight increase in platelet count, but no change in platelet factor 4, platelet aggregation ratio, recalcification, and prothrombin time. Repeated bouts of maximum exercise associated with acidosis caused a significant increase in platelet count, platelet factor 4 release, and strong intensification in fibrinolytic activity.[42] Physical conditioning has been shown to enhance the fibrinolytic response to exercise in healthy men in a manner directly related to intensity of their activity. Thus marathon runners had increases in fibrinolytic activity of 76% with exercise compared with 63% for joggers and 55% for sedentary persons. They also found that packed cell volume, red cell count, platelets, and white cell count all increased significantly with exercise but like us, found no differences in resting packed cell volume resting red cell count, or red cell indices.[7]

Acute exercise has not been shown to affect fibrinogen, factor V, factor VII or factor X concentrations.[9] Factor VII concentrations have been shown to correlate positively with dietary fat[32] and with plasma cholesterol and triglyceride concentrations.[43] We did not give our patients specific dietary advice, and therefore are unable to exclude dietary variations as a factor in the difference in factor VIIc concentrations. Lipoprotein analyses are yet to be correlated with factor VIIc concentrations. The rise in factor VII concentrations among the aerobic trained group is disappointing. It could offset the benefits of low fibrinogen concentrations, but unlike that for fibrinogen, which is linear for non-fatal ischaemic heart disease,[44] we do not know the exact relation between factor VII and cardiovascular risk. It is impossible to comment meaningfully on data we did not collect, that is influences of diet on factor VII concentrations in these men. Data are available on weight at entry and follow up (table 6). Body weight or mean skin fold thickness did not alter significantly in any of the groups during the period of assessment. Body weight would no more account for the changes in fibrinogen, lack of effect on factor VII, and improved treadmill performance than would smoking habit or drug history.

Fibrinogen concentrations are higher in smokers than in non-smokers, but this would not account for the differences we found in our patients. Fibrinogen may exert its effects on incidence of coronary artery disease through plasma viscosity or thrombogenesis. It is also a determinant of platelet behaviour. Concentrations within the physiological range have a noticeable and consistent effect on measures of the ability of platelets to aggregate, and also influence blood viscosity.[32,44]

Table 6 Body weight at each assessment (mean (SEM))

	Baseline (kg)	*3 months (kg)*	*6 months (kg)*
Control	71·9 (2·4)	73·0 (2·5)	73·4 (2·3)
Aerobic	72·8 (2·7)	73·6 (2·7)	74·1 (2 8)
Power	72·6 (1·6)	72·3 (1·5)	72·7 (1·5)

Beneficial effects of power exercise training in this group were delayed. This would suggest that for immediate rehabilitation, aerobic exercise may be better. Most activities of daily living, however, involve a power component—for example, gardening, DIY, and shopping so power training is a relevant part of rehabilitation programmes.

We did not study the effects of acute exercise on haemostatic factors either in training or on the treadmill. Several previous studies have considered the issue with variable results. We do not know what the effects antiplatelet or anti-ischaemic drugs have on haemostatic factors but our groups did not have significant differences in drug history.

It has been difficult to date to explain fully the beneficial effects of exercise on health. We often allude to other changes in behaviour of exercise trained subjects to account for these benefits. In our study, we have two exercise trained groups showing differences in both treadmill time and haemostatic factors despite attending sessions in the same place under supervision of the same persons and receiving the same treatment in all ways other than the type of exercise they performed. We cannot help but conclude (no matter what the precise mechanism is) that aerobic exercise training results in different and earlier benefits than power exercise training in these patients.

LIMITATIONS OF THE STUDY

Cardiopulmonary exercise testing could have improved the objectivity of the study with regard to exercise capacity. Unfortunately we did not have the necessary equipment. Motivation of patients plays a large part in exercise rehabilitation and its evaluation, and it is difficult to quantify the extent to which this is so without measures of maximum oxygen uptake and anaerobic threshold. Differences obtained, however, were sufficiently large between the exercise groups and controls to justify the use of treadmill exercise testing in the assessment of both types of exercise.

We did not measure plasma viscosity or other haemorrheological factors known to influence coronary artery disease although fibrinogen even in the physiological range, is known to affect platelet activity and plasma viscosity.

In summary, exercise training can increase the benefits of coronary artery surgery. Power training may be as effective as aerobic training and carries no special dangers but its benefits may be slower to start. Aerobic exercise training causes a significant fall in fibrinogen concentrations. Power training exerts a delayed and small beneficial influence on factor VII concentrations. The mechanisms of these influences and differences are worthy of further investigation.

It would be a matter of great speculation to try to predict the degree of reduction of risk of ischaemic heart disease achieved by the fall in fibrinogen concentration after aerobic exercise training. To find such a predictive factor, a larger and longer study than this would be needed. It is possible, however, to infer (from previous epidemiological studies) that a significant reduction in cardiac events can be expected from the fall in fibrinogen concentration achieved by our patients after aerobic exercise training. The results we have found await confirmation and long-term follow up of cardiovascular events in such a group of patients.

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Jugular venous 'a' wave in pulmonary hypertension: new insights from a Doppler echocardiographic study

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Abstract

***Objective*—To study the mechanisms underlying the dominant 'a' wave seen in patients with primary pulmonary hypertension.**

***Design*—Retrospective and prospective examination of the jugular venous pulse recording, flow in the superior vena cava, and Doppler echocardiographic studies.**

***Setting*—A tertiary referral centre for both cardiac and pulmonary disease, with facilities for invasive and non-invasive investigation, and assessment for heart and heart-lung transplantation.**

***Patients*—12 patients with primary pulmonary hypertension, most being considered for heart-lung transplantation.**

***Results*—Two distinct patterns of venous pulse and superior vena caval flow were identified: a dominant 'a' wave with no 'v' wave, an absent or poorly developed 'y' descent, and exclusively systolic downward flow in the superior vena cava (group 1, n = 8), and a dominant 'v' wave, deep 'y' descent and exclusively diastolic downward flow in the superior vena cava (group 2, n = 4). A comparison between the two groups showed age (mean (SD)) 42 (18) *v* 36 (7) years, RR interval 700 (65) *v* 740 (240) ms, left ventricular end diastolic dimension 3·6 (0·8) *v* 3·2 (1·0) cm and end systolic dimension 2·1 (0·5) *v* 2·3 (0·3) cm, right ventricular end diastolic dimension 2·6 (0·5) *v* 2·8 (0·6) cm, and pressure drop between right ventricle and right atrium 60 (8) *v* 70 (34) mm Hg to be similar. Duration of tricuspid regurgitation 520 (30) *v* 420 (130) ms and the time interval of pulmonary closure to the end of the tricuspid regurgitant signal 140 (30) *v* 110 (40) ms were longer in group 1 compared with group 2, whereas right ventricular filling time was much shorter 180 (70) *v* 350 (130) ms. In seven patients from group 1, a single peak of forward tricuspid flow was present, but this pattern was seen in only one patient from group 2.**

***Conclusions*—In patients with primary pulmonary hypertension, the apparent 'a' wave seen in the venous pulse is, in fact, a summation wave. It is probably the result of large pressure changes that must underlie rapid acceleration and deceleration of blood across the tricuspid valve when the right ventricular filling time is short.**

(*Br Heart J* 1992;68:187–91)

A dominant 'a' wave in the venous pulse is universally attributed in current textbooks of cardiology to an increase in the resistance to atrial emptying.[1–3] In the absence of any abnormality at the level of the tricuspid valve, the primary abnormality is described as a reduction in right ventricular compliance.[4] We found an entirely different mechanism underlying the dominant 'a' wave seen in a substantial minority of patients with dilated cardiomyopathy, in whom right ventricular filling time was greatly reduced by prolonged tricuspid regurgitation.[5] A dominant 'a' wave, however, in such patients has not been widely recognised, at any rate since the work of Mackenzie,[6] and there seemed to be no reason to suppose that such an unorthodox mechanism would be seen outside these rather special circumstances. Thus it seemed of interest to use similar echocardiographic, Doppler, and graphical methods to study an 'a' wave with well recognised associations, and to compare the underlying mechanisms with those seen in dilated cardiomyopathy. There was, we thought, no 'a' wave more typical in its genesis, than that associated with primary pulmonary hypertension.

Patients and methods

PATIENTS

We studied 12 patients with primary pulmonary hypertension, most of whom were being considered for heart-lung transplantation. Their ages ranged between 24 and 57 years and 10 were women. All were in sinus rhythm, and in all, the venous pressure was increased on clinical examination.

M MODE ECHOCARDIOGRAMS

M mode echocardiograms of the right and left ventricular cavities were made with reference to the cross sectional display on an ATL imager Mk 300I. The left parasternal view was used with the patients in the left lateral position. All M modes were recorded photographically at a paper speed of 10 cm/s on Honeywell equipment with simultaneous

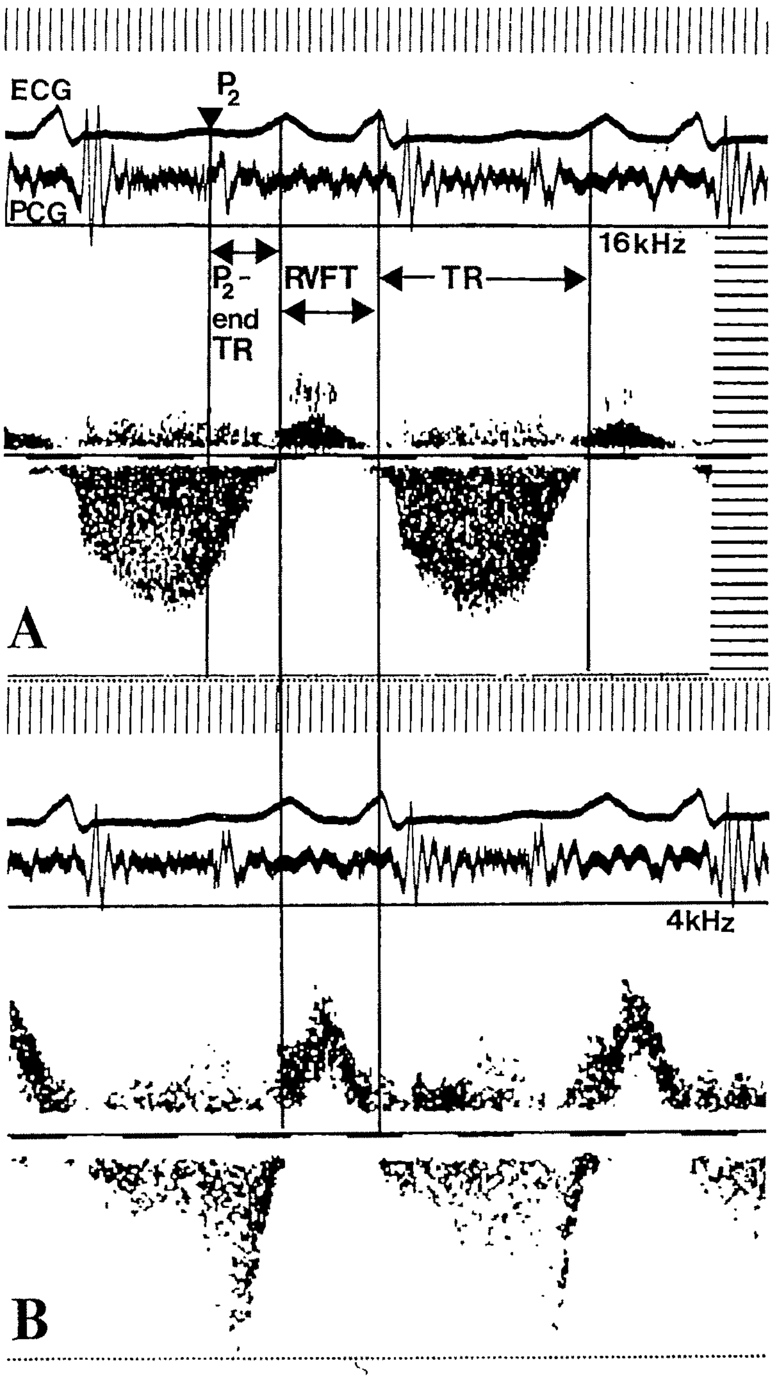

Figure 1 (A) Continuous wave Doppler recording of tricuspid regurgitation and (B) pulsed wave Doppler recording of forward tricuspid flow. Both recordings are made with simultaneous electrocardiogram and phonocardiogram, and the Doppler calibrations are indicated. Pulmonary closure (P_2) is indicated, and the time intervals of P_2 to the end of tricuspid regurgitation, right ventricular filling time, and tricuspid regurgitation duration are shown. ECG, electrocardiogram; PCG, phonocardiogram; P_2, pulmonary closure; P_2-end TR, time interval from pulmonary closure to the end of the tricuspid regurgitation signal; RVFT, right ventricular filling time; TR, tricuspid regurgitation duration.

phonocardiogram and electrocardiogram. The internal dimensions of left and right ventricles were measured at the start of the Q wave of the electrocardiogram. The identity of P_2, normally the start of the second component of the second heart sound, was routinely checked against the time of closure of the pulmonary valve, or the valve closure artefact at the end of pulmonary ejection on the pulsed Doppler record.

DOPPLER ECHOCARDIOGRAPHY

Doppler recordings were made with Doptek equipment, and a 2 MHz transducer. Retrograde flow across the tricuspid valve during systole was detected in continuous mode and forward flow velocities across the valve during diastole in pulsed mode (fig 1). Flow velocities in the superior vena cava were made from the right supraclavicular fossa in continuous mode with the transducer directed towards the right atrium. All recordings were made at a paper speed of 10 cm/s, with simultaneous phonocardiogram and electrocardiogram. From the record of tricuspid regurgitant flow, peak systolic frequency shift was obtained, and thus peak ventriculoatrial pressure drop was calculated from the modified Bernoulli equation. The time interval from P_2 to the end of the regurgitant flow was taken as the relaxation time of the right ventricle, and the interval between the end of one pulse of tricuspid regurgitation and the start of the next as the filling time of the right ventricle (fig 1). On the pulsed Doppler record of forward flow, peak velocities during early diastole (E wave), and atrial systole (A wave) were noted. If only a single flow velocity pulse was present, with the start of early diastolic flow occurring after the P wave of the succeeding beat, we referred to the filling pattern as summation. On the superior vena caval Doppler, we noted whether flow velocities towards the right atrium were greater during ventricular systole ('x' descent flow), or early diastole ('y' descent flow).

JUGULAR VENOUS PULSE

The jugular venous pulse was recorded with a Cambridge pulse transducer (time constant 4 s) from the position on the neck where it was most apparent clinically. Where possible, simultaneous venous pulse records and records from the superior vena cava were made. The dominant wave, whether 'a' or 'v', was noted. In those patients with a dominant 'v' wave, the increase in the venous pulse above its minimum level at the start of the Q wave of the electrocardiogram was noted, and expressed as a proportion of the total excursion during the cardiac cycle.

STATISTICAL ANALYSIS

Values are given as mean (SD). The possible statistical significance of differences between mean values was examined using Student's *t* test, and $p < 0{\cdot}05$ was taken as significant.

Results

In eight patients (group 1), the jugular venous pulse showed a dominant 'a' wave (fig 2). In general, no 'v' wave at all was present, and the 'y' descent was either absent or poorly developed. In all these patients, downward flow in the superior vena cava occurred exclusively during ventricular systole, being complete before P_2. In the remaining four patients (group 2), there was a dominant 'v' wave in the venous pulse. Peak venous pressure occurred late during ventricular systole, and there was a

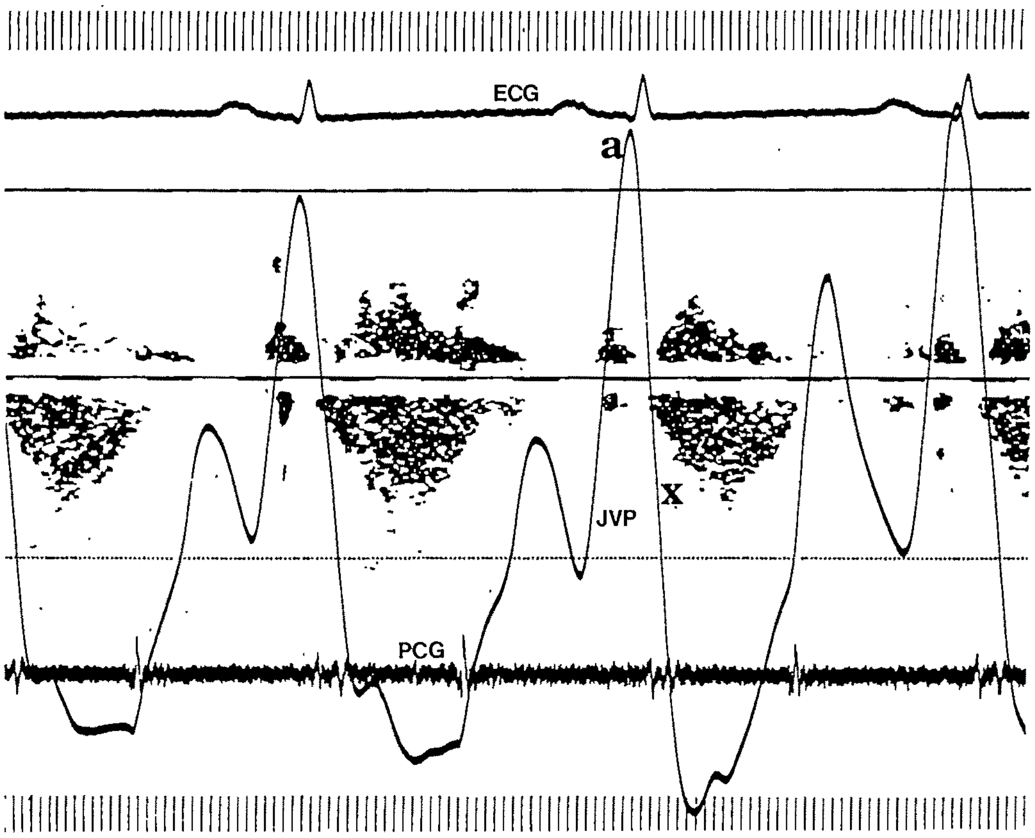

Figure 2 Jugular venous pulse recording with simultaneous electrocardiogram and phonocardiogram, with pulsed Doppler of superior vena caval flow. Note the dominant 'a' wave in the venous pulse with an 'x' descent and systolic downward vena caval flow. JVP, jugular venous pulse; ECG, electrocardiogram; PCG, phonocardiogram. Doppler calibration: full scale deflection = 2 kHz.

deep 'y' descent which started at about the same time as P_2 (fig 3). In all these patients, flow from the superior vena cava towards the right atrium was found only during diastole. In three of these cases, the venous pressure rose mainly during systole, and in the fourth before the QRS complex of the electrocardiogram, suggesting a diastolic origin.

ASSOCIATION BETWEEN VENOUS PULSE AND RIGHT SIDED EVENTS

Because no patient had an intermediate pattern of either venous pressure or superior caval flow, those with a dominant 'a' wave (group 1) were compared with those with a dominant 'v' (group 2 and table). No significant difference was found between the two groups for age,

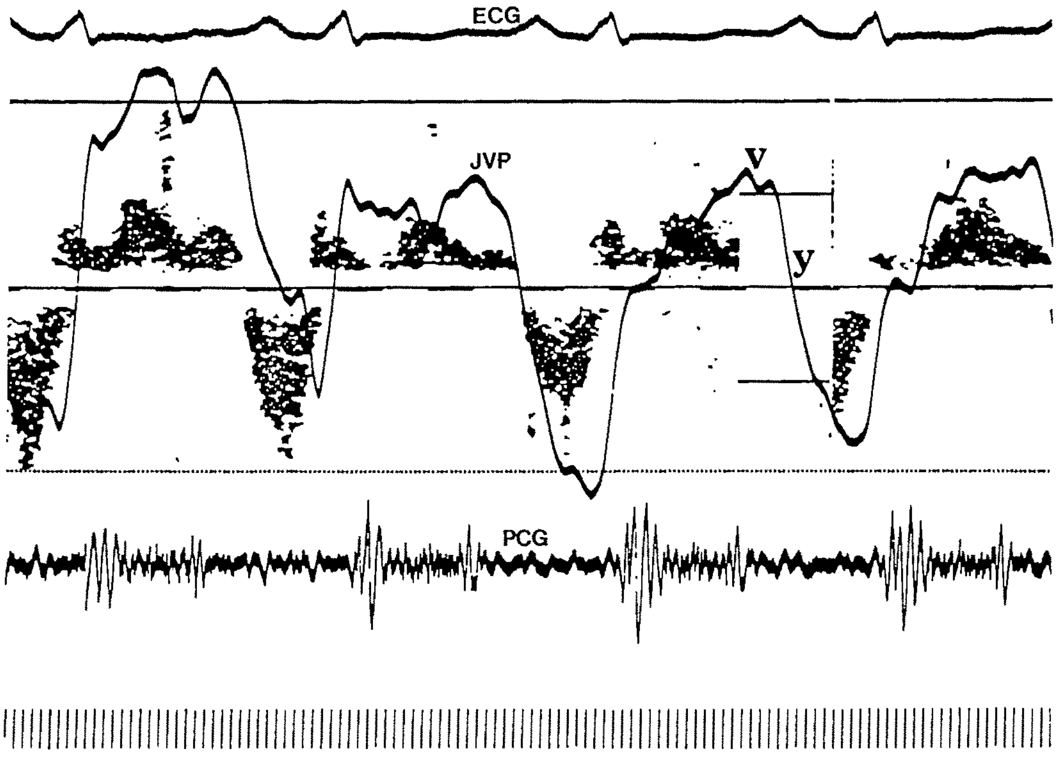

Figure 3 Jugular venous pulse recording with simultaneous electrocardiogram and phonocardiogram, with pulsed Doppler of superior vena caval flow. Note the dominant 'v' wave in the venous pulse with a 'y' descent and diastolic downward vena caval flow. JVP, jugular venous pulse; ECG, electrocardiogram; PCG, phonocardiogram. Doppler calibration: full scale deflection = 2 kHz.

Jugular venous pulse pattern and associated characteristics (mean (SD)) in patients with primary pulmonary hypertension

Variable	*Group 1 Dominant 'a' wave (n=8)*	*Group 2 Dominant 'v' wave (n=4)*
Age (y)	42 (18)	36 (7)
RR interval (ms)	700 (65)	740 (240)
LV EDD (cm)	3·6 (0·8)	3·2 (1·0)
LV ESD (cm)	2·1 (0·5)	2·3 (0·3)
RV EDD (cm)	2·6 (0·5)	2·8 (0·6)
RV-RA pressure drop (mm Hg)	60 (8)	70 (34)
Duration of tricuspid regurgitation (ms)	520 (30)*	420 (130)
RV filling time (ms)	180 (70)**	350 (130)
Pulmonary closure—end of tricuspid regurgitant signal (ms)	140 (30)*	110 (40)

*$p < 0\cdot05$ *v* group 2; **$p < 0\cdot01$ *v* group 2. EDD, end diastolic dimension; ESD, end systolic dimension; LV, left ventricle; RA, right atrium; RV, right ventricle.

heart rate (measured as RR interval), left or right ventricular transverse dimensions, or peak pressure drop from right ventricle to right atrium estimated from the peak velocity of tricuspid regurgitation, and no patient had diastolic tricuspid regurgitation. There were significant differences, however, in the relative timing of the systolic tricuspid regurgitation. In patients with a dominant 'a' wave, the whole regurgitant signal was more prolonged, as was that part after pulmonary valve closure (both $p < 0\cdot05$), and even more significant, right ventricular filling time was little more than half that in patients with a dominant 'v' wave ($p < 0\cdot01$). This difference was reflected in the forward tricuspid flow velocity pattern. In seven out of the eight patients with a dominant 'a' wave, there was only one peak, representing superimposed early diastolic and atrial components. By contrast, this pattern was seen in only one of those patients with a dominant 'v' wave, the rest having a dominant E wave.

Discussion

An increase in atrial activity is widely regarded as a homoeostatic mechanism, which maintains stroke volume in the presence of ventricular disease. Some disturbance of diastolic function—impaired compliance is often invoked—causes the component of stroke volume entering early in diastole to fall, and that during atrial systole, to be correspondingly increased. On the left side of the heart, this is associated with a dominant 'a' wave on the transmitral flow velocity trace, and often with a fourth heart sound. On the right side of the heart, exactly similar mechanisms have been invoked as the basis of the dominant 'a' wave often found in the venous pulse.[1 2 4] The conditions thought to give rise to such an 'a' wave are found most typically in primary pulmonary hypertension. An overloaded right ventricle becomes hypertrophied; its diastolic properties are impaired, and in the absence of atrial or ventricular septal defect, increased right atrial activity shows itself as an increased pressure wave in the venous pulse. For these reasons, we took the condition as a paradigm of right ventricular overload to study interrelations between pressure and flow in more detail.

Our results confirmed these widely accepted ideas to the extent that a dominant presystolic wave is often present in the venous pulse of patients with primary pulmonary hypertension, but in almost every other respect they were incompatible. In seven out of the eight patients with such a wave, we found no evidence of reduced early diastolic flow across the tricuspid valve, nor a compensatory increase during atrial systole. Instead we found a single summation wave, in which early diastolic and atrial systolic components were superimposed. This pattern was the result of ventricular filling time being shortened to a mean value roughly half that seen in the rest of the patients, although heart rate was not significantly different. When filling time is short, stroke volume is only maintained if the velocity of blood flow into the ventricle is increased; this requires correspondingly high values of acceleration and deceleration.[7] Acceleration of blood only occurs as the result of a pressure gradient. We suggest, therefore, that the presystolic pressure wave seen in the venous pulse of these patients is not the result simply of the effects of right atrial systole. Rather, it is the clinical manifestation of the pressure changes that must underlie the rapid acceleration and deceleration when filling time is short. It is thus better termed a summation wave, to stress its relation to the timing of intracardiac events.

When right ventricular filling time was longer, right sided events were different. The tricuspid forward flow velocity trace showed a dominant E wave in three patients and a single wave in one; in no case was there a dominant 'a' wave. At the same time, the venous pulse showed a dominant 'v' wave and 'y' descent. These fundamental differences could not be attributed to age, heart rate, the size of the cavity of either right or left ventricle, or the drop in systolic pressure between right ventricle and right atrium. Rather, the reason why filling time was longer was that the overall duration of the tricuspid regurgitation was less. The main factor determining the duration of tricuspid regurgitation is peak right ventricular pressure[8]; however, right ventricular disease might have further prolonged it in patients with a dominant 'a' wave, possibly by slowing relaxation. Alternatively, some process might have shortened the tricuspid regurgitation in patients with a dominant 'v' wave. On the left side of the heart, the duration of the mitral regurgitation falls as its severity increases,[9] and we have previously suggested that the same process might act on the right side of the heart.[10] In line with this explanation is the systolic form of the venous pulse in three of four patients, and the appearance of retrograde systolic flow in the superior vena cava (fig 3). We suggest, therefore, that in patients with a dominant 'v' wave, the tricuspid regurgitation was haemodynamically significant instead of being merely functional. The dominant E wave on the transtricuspid flow pulse does not necessarily reflect normal diastolic properties within the right ventricle; the striking drop in filling pressure associated with it strongly suggested that it had become normalised.

A characteristic chain of cause and effect can thus be seen to underlie a dominant presystolic wave in the venous pulse of patients with primary pulmonary hypertension. The pressure wave is the direct result of a summation filling pattern due to a short filling period requiring increased acceleration and deceleration rates of blood flow. Right ventricular filling time is short because functional tricuspid regurgitation is prolonged, and we have previously shown this prolongation to be the predictable consequence of a high systolic pressure in the right ventricle.[8] When filling time is longer, and transtricuspid flow shows early diastolic and atrial components, the dominant 'a' wave is no longer present. Also, during the period when right ventricular tension is still decaying the mitral valve has already opened although the left ventricular filling pattern is disturbed, with reduced E wave and increased A wave velocities.[11] Thus the effect of atrial systole is indeed accentuated in patients with pulmonary hypertension, but on the left rather than on the right side of the heart. Finally, the mechanism underlying the presystolic jugular venous wave seen in our patients did, in fact prove to be similar to that previously described as occurring in patients with dilated cardiomyopathy.[2] In such patients, however, right ventricular pressures were much lower, suggesting that the prolonged tricuspid regurgitation was caused by some other mechanism, possibly primary right ventricular disease.

This analysis suggests that the traditional ideas about right sided haemodynamics in pulmonary hypertension may have to be modified. At the same time, it stresses the scope of combined graphical and Doppler techniques in delineating disturbed physiology, and suggests new approaches to its pharmacological palliation. Whereas heart-lung transplantation may be the ultimate treatment for these patients, the severe shortage of donor material and the less satisfactory survival of patients after this operation than after isolated cardiac transplantation, both suggest a constructive role for delaying surgery by appropriate medical management.

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Continuous wave Doppler echocardiography after surgical repair of coarctation of the aorta

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Abstract

***Objective*—To find how closely pressure gradients across the aortic arch derived from Doppler echocardiography reflect gradients measured by catheter after surgical repair of coarctation of the aorta.**

***Design*—Pressure drop across the aortic arch was measured simultaneously by continuous wave Doppler and double lumen catheter in 20 patients with repaired coarctation of the aorta.**

***Results*—The peak pressure drop estimated by Doppler was almost invariably higher than the peak to peak gradient measured by catheter, as might be expected. Wide variation was seen between the Doppler measured pressure drop and instantaneous peak gradient measured by catheter, ranging from +22 to −17 mm Hg. The reasons for these differences are unclear but are probably related to a combination of complex flow dynamics in the aortic arch, difficulty in closely aligning the Doppler beam with flow, and inability to measure flow velocity immediately proximal to the site of the surgical repair with continuous wave Doppler.**

***Conclusions*—Continuous wave Doppler echocardiography may significantly overestimate or underestimate the pressure drop after repair of coarctation and it should be interpreted with caution in individual patients. Catheterisation with angiography remains the reference standard for assessment of surgical repair of the aortic arch.**

(*Br Heart* 1992;68:192–4)

Doppler ultrasound has become an established technique for assessment of obstructive lesions with the modified Bernoulli equation (pressure drop = 4 × the square of peak flow velocity).[1] Pressure gradients derived from Doppler in untreated coarctation of the aorta may be less reliable than similar calculations for valve stenosis,[2-4] particularly in the presence of an arterial duct[5] or collateral circulation.[6] Some doubt has also been cast on the meaning of increased flow velocity across the aortic arch after surgical repair.[7]

Having sometimes noted increased flow velocities in the descending aorta after apparently satisfactory repair of coarctation, we undertook to investigate the accuracy of continuous wave Doppler and the modified Bernoulli equation in patients who had undergone surgical repair of coarctation.

Patients and methods

We studied prospectively 20 patients aged between 4·7 and 33 (mean (SD) 15·5 (5·3)) years with repaired coarctation of the aorta. Catheterisation was carried out either as part of routine late postoperative review of patch aortoplasty or clinical suspicion of residual or recurrent coarctation. At catheterisation, the ascending and descending aortic pressures were measured simultaneously with a fluid filled, thin walled, French 8 double lumen catheter. Before placing the catheter across the aortic arch simultaneous pressures from the two lumens in the descending aorta were recorded to ensure that identical waveforms were obtained. The pressure waveforms from either side of the aortic arch were recorded at 100 mm/s paper speed and were digitised on a graphics pad to compute the peak and peak to peak pressure gradient. A total of five pressure waveforms were digitised and the maximum values taken for comparison with the Doppler derived gradient.

During the recording of the pressures peak flow velocity in the descending aorta was measured with a dedicated continuous wave Doppler transducer positioned in the suprasternal notch. The highest peak flow velocity was recorded and the modified Bernoulli equation (four times the square of the peak velocity) was used to calculate the peak pressure drop for comparison with the catheter measurements. The agreement between the catheter and Doppler derived gradients was compared by the method of Bland and Altman.[8]

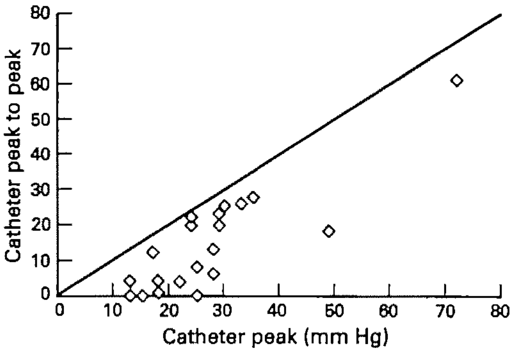

Figure 1 Scatter plot (with line of identity shown) illustrating the differences between peak and peak to peak pressure drop measured by double lumen catheter. Instantaneous peak values are all higher than peak to peak measurements, but the difference between the two measurements varies considerably in individual patients.

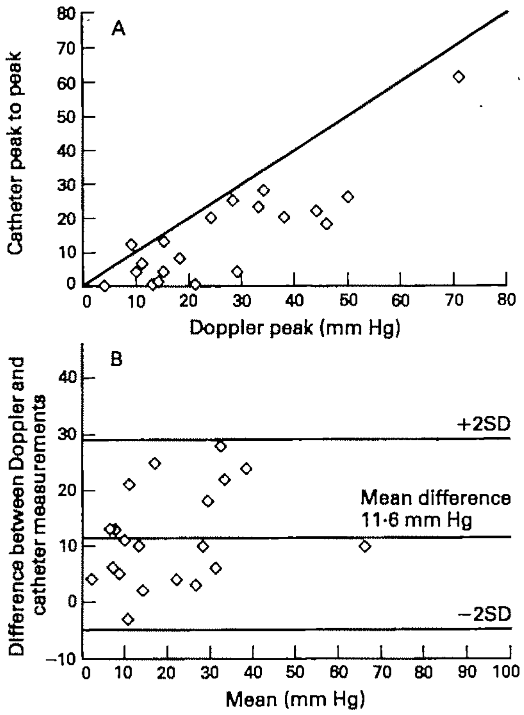

Figure 2 Comparisons of Doppler estimated peak pressure drop and peak to peak gradient measured by catheter. (A) Scatter plot suggests a similar relation between the two measurements to that shown in fig 1. Line of identity as in fig 1. (B) Data expressed by the method of Bland and Altman.[8] Mean of the two measurements is plotted against the difference between Doppler estimated gradient and catheter peak to peak gradient. Doppler gradient was on average 11·6 mm Hg (8·7) higher than catheter peak to peak gradient (range of difference between the two measurements +2 s to −3 mm Hg).

Results

The figures illustrate the relations between the two gradients measured by catheter and between Doppler and catheter derived measurements. As might be expected, instantaneous peak catheter gradient was invariably higher (mean (SD) 12·6 (7·6), range 2 to 31 mm Hg) than catheter measured peak to peak gradient, although the difference between the two measurements was inconsistent (fig 1). A similar, also inconsistent, relation was seen between Doppler peak and catheter peak to peak gradients, the mean difference between the two being 11·6 (8·7) and the range +28 to −3 mm Hg (fig 2).

Much closer overall agreement was seen between the Doppler gradient and the catheter instantaneous peak gradient. The mean difference between these two measurements was 0·9 (10) mm Hg, but the individual differences ranged from +22 to −17 mm Hg (fig 3).

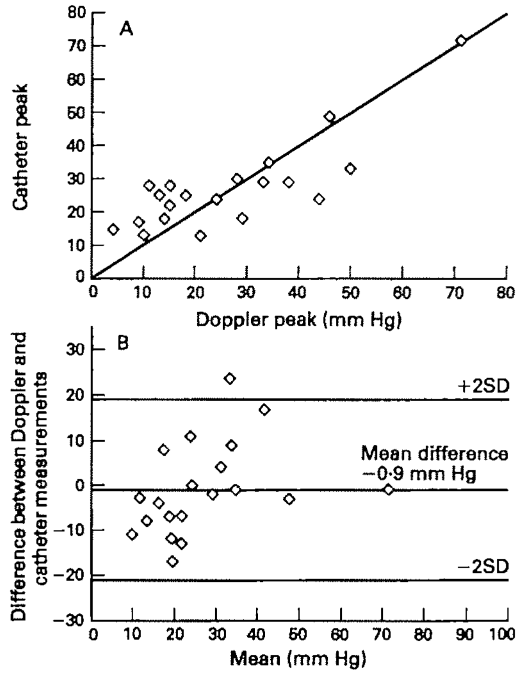

Figure 3 Comparisons of Doppler measured gradient and catheter peak gradient. (A) Scatter plot (with line of identity shown) suggests a closer overall relation between these two measurements. (B) Data expressed by the method of Bland and Altman.[8] The closer overall agreement between these two measurements (compared with those in fig 1) is confirmed, the average difference between Doppler and catheter values being only 0·9(10) mm Hg. The data points, however, show that in an individual patient the Doppler may overestimate the true peak gradient by as much as 22 mm Hg or underestimate it by as much as 17 mm Hg.

Discussion

The inconsistent relation between instantaneous peak and peak to peak gradient seen in aortic stenosis[9] appears equally important when assessing pressure gradient across repaired coarctation of the aorta. Disappointingly, however, even when this is taken into account, the use of continuous wave Doppler and the modified Bernoulli equation may still result in substantial overestimation or underestimation of the peak pressure gradient.

The use of a dedicated continuous wave Doppler transducer alone results in difficulty in measuring flow velocity proximal to the site of the aortic repair. In practice this velocity is often less than 1 m/s and may be safely ignored in the calculation of pressure drop but if this proximal flow velocity is greater than 1 m/s, excluding it from the modified Bernoulli equation may result in some overestimation of the pressure gradient. Ideally, therefore, flow velocity in the proximal descending aorta should be measured separately[1 2 7] although close alignment with flow in this part of the arch may be difficult.[1] Underestimation of pressure drop is most likely to be due to poor alignment of the Doppler beam with the direction of blood flow, a problem that may be minimised but not eliminated by technical expertise during the examination. Further sources of error may lie in the application of the modified Bernoulli equation to potentially complex flow dynamics in an aortic arch distorted by surgical intervention, or scarring, or with long segment stenosis.[10] Combined measurement of other Doppler values such as diastolic velocity decay[4 11 12] may enhance detection of important aortic arch obstruction, but even this may be unreliable when extensive collateral circulation has developed.[6]

Previous reports of measurements of nonsimultaneous ultrasound and catheter pressure have suggested that Doppler gradient closely predicts catheter gradient.[1 2] Our study of simultaneous catheter and Doppler measurements shows that continuous wave Doppler may considerably underestimate or overestimate aortic arch pressure gradient after surgical repair of the arch and that Doppler ultrasound should be interpreted with caution in this setting. The clinical implication of our findings is that modest increases of flow velocity in the aortic arch after repair of coarctation should not be acted upon without careful consideration of other factors such as the rate of the velocity decay[11] and the findings on clinical examination at rest and, ideally, during exercise.[12] Our present practice is to have a low threshold for invasive investigation if the flow velocity in the descending aorta exceeds 3 m/s with diminished femoral pulses, with or without upper limb hypertension.

Aortography remains the reference standard for postoperative assessment of aortic arch repair.

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Optimal pacing modes after cardiac transplantation: is synchronisation of recipient and donor atria beneficial?

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Abstract

***Objective*—To investigate the response of the transplanted heart to different pacing modes and to synchronisation of the recipient and donor atria in terms of cardiac output at rest.**

***Design*—Doppler derived cardiac output measurements at three pacing rates (90/min, 110/min and 130/min) in five pacing modes: right ventricular pacing, donor atrial pacing, recipient-donor synchronous pacing, donor atrial-ventricular sequential pacing, and synchronous recipient-donor atrial-ventricular sequential pacing.**

***Patients*—11 healthy cardiac transplant recipients with three pairs of epicardial leads inserted at transplantation.**

***Results*—Donor atrial pacing (+11% overall) and donor atrial-ventricular sequential pacing (+8% overall) were significantly better than right ventricular pacing ($p < 0.001$) at all pacing rates. Synchronised pacing of recipient and donor atrial segments did not confer additional benefit in either atrial or atrial-ventricular sequential modes of pacing in terms of cardiac output at rest at these fixed rates.**

***Conclusions*—Atrial pacing or atrial-ventricular sequential pacing appear to be appropriate modes in cardiac transplant recipients. Synchronisation of recipient and donor atrial segments in this study produced no additional benefit. Chronotropic competence in these patients may, however, result in improved exercise capacity and deserves further investigation.**

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Permanent pacemaker insertion may be necessary after cardiac transplantation for the treatment of sinus node dysfunction or complete heart block. Rates of pacemaker implantation vary in reported series from 4%-24%.[1-3] Our data suggest that only those patients with sinus node dysfunction will require long-term pacing, and these may comprise fewer than 2% of cardiac transplant recipients.[2] Although the number of patients needing long-term pacing may thus be small, for those who do need pacing the optimal mode should be used to realise the maximum potential of the transplanted heart. Although physiological pacing has been shown to be haemodynamically better than ventricular pacing in the native heart,[4-6] this may not necessarily be the case after transplantation.

The surgical technique of orthotopic cardiac transplantation has changed little since first described by Cass and Brock in 1959.[7] Donor atria are sutured to recipient atrial remnants to form a pair of composite atria, the two components of each composite atrium being electrically isolated. Thus donor and recipient atrial systole are independent with resultant incoordinate atrial contraction. Few data are available on the haemodynamic contribution of atrial contraction to ventricular filling in transplanted hearts. We have noted a decreased active atrial contribution to left ventricular filling in transplant recipients compared with normal subjects (data submitted for publication) and others have shown an increase in peak Doppler transmitral velocity in late diastole with coincidental recipient and donor atrial systole.[8] These findings suggest altered left ventricular filling after cardiac transplantation; left ventricular output (that is, cardiac output) may thus not reach its full potential.

Physiological pacing is recommended for many patients with native hearts.[9] The benefits are twofold: improved exercise tolerance compared with ventricular pacing,[10] and reduced likelihood of pacemaker syndrome.[11] Although the second may also be true in transplant recipients, pacing one part of the atrium (donor) may not be more beneficial in terms of improved cardiac function in the transplanted heart than ventricular pacing.

Coordination of the atrial components by electrical connection is theoretically attractive and has been described in one patient.[12] As well as atrial synchrony, another theoretical benefit of electrical atrial connection is chronotropic competence in the transplanted heart in response to neural stimuli to the recipient sinus node.

The aims of this study were (*a*) to investigate conventional pacing modes in the transplanted heart, and (*b*) to compare conventional physiological pacing with synchronous recipient-donor atrial physiological pacing.

Patients and methods

After ethical approval at our hospital, all cardiac transplant recipients had three pairs of epicardial pacing wires inserted at transplantation—to recipient right atrium, donor right atrium and right ventricle. Subsequent study of these patients was dependent on several criteria. Patients had to be (*a*) well and able to give informed consent, (*b*) not on inotropes, (*c*) within 48 hours of a normal cardiac biopsy, and (*d*) in sinus rhythm with normal atrioventricular conduction.

CARDIAC PACING

Epicardial cardiac pacing was performed through an external dual chamber pacing generator. Patients were paced in a random sequence in each of five modes where possible —namely, ventricular pacing alone, donor atrial pacing, synchronous recipient-donor atrial pacing, conventional donor atrial and sequential ventricular pacing, and synchronous recipient-donor atrial and sequential ventricular pacing. Three pacing rates were used for our investigation—90 per minute, 110 per minute, and 130 per minute. As heart transplant recipients have a high basal heart rate (due to denervation), 90 per minute was chosen as our basal rate, with 110 and 130 per minute to reflect rates expected in normal subjects with exercise. For AV sequential pacing, the AV delay was set at 200 ms unless normal conduction occurred necessitating a shorter delay. In an individual patient this delay was maintained constant at all pacing rates and in both AV sequential modes.

DOPPLER MEASUREMENT OF CARDIAC OUTPUT

Cardiac output was determined non-invasively by a previously validated technique by Doppler echocardiography.[13] Continuous wave Doppler waveforms were obtained from the ascending aorta with Hewlett-Packard echocardiographic equipment. Flow velocity integrals were found by two observers who traced from the baseline around the velocity curve with a digitising tablet linked to a microcomputer.[14] Ten waveforms were measured blindly in each mode and at each pacing rate. Aortic valve dimensions were measured with cross sectional echocardiography with cardiac output derived by the formula:

cardiac output = stroke distance × heart (pacing) rate

(where stroke distance = aortic valve area × Doppler velocity integral).

Statistical analysis was by paired t tests.

Results

PATIENTS

Of 21 consecutive patients who had three pairs of epicardial pacing wires placed at transplantation, only 11 met our inclusion criteria for further study. These 11 patients (10 men) were investigated within 21 days of transplantation. The mean age of the recipients was 45 (range 18–53), with a mean donor age of 27 (range 15–47). All patients were in sinus rhythm with right bundle branch block (four patients) or had an RSR′ pattern with a QRS duration within normal limits (seven patients). Two patients had resting heart rates above 90 per minute during part or all of the pacing study. Pacing was not possible in all pacing modes in all patients because of various difficulties including basal rates above 90 per minute, induction of extrasystoles, and failure to capture, especially with synchronous atrial pacing. Thus of 165 possible combinations in our 11 patients, 49 were not carried out. The results are presented according to the number of patients in whom comparisons were possible, and hence the mean values for cardiac output in the same pacing mode between these comparisons differ. To obviate statistical problems with small numbers, and to confirm that the individual differences between pacing modes at different pacing rates were correct, we have averaged all measurements from the different rates obtained in a pacing mode to obtain an overall mean value for cardiac output in that mode. This allows statistical comparison between the pacing modes.

CONVENTIONAL PACING MODES

Both donor right atrial pacing and conventional AV sequential pacing were better than right ventricular pacing in our patients (table 1). The increase in cardiac output found with donor right atrial pacing compared with right ventricular pacing was +13% at 90 per minute, +10% at 110 per minute, and +11% at 130 per minute. Overall from 27 comparisons, the benefit was +11%. The increase in cardiac output with conventional AV sequential pacing compared with right ventricular pacing was +9%, +7%, and +8% respectively at the pacing rates studied, and +8% overall from 24 comparisons. The difference between donor atrial pacing and conventional AV sequential pacing was small at all rates (2·85% to 3·30% in favour of donor atrial pacing), but this was not significant even with overall means from 24 observations.

Table 1 Comparison of conventional pacing modes

	DA	*RV*		*D-V*	*RV*		*DA*	*D-V*	
Pacing rate									
90/min	7·30 (1·80)	6·46 (1·70)	$p < 0·02$ (n=8)	6·80 (1·43)	6·24 (1·53)	$p < 0·01$ (n=8)	6·93 (1·59)	6·71 (1·52)	NS (n=7)
110/min	8·28 (2·04)	7·54 (2·15)	$p < 0·02$ (n=9)	8·08 (2·22)	7·54 (2·30)	$p < 0·01$ (n=8)	8·31 (2·03)	8·08 (2·08)	NS (n=9)
130/min	9·45 (2·57)	8·54 (2·51)	$p < 0·05$ (n=10)	8·85 (2·98)	8·22 (2·62)	$p < 0·02$ (n=8)	9·14 (2·39)	8·85 (2·98)	NS (n=8)
Mean	8·42 (2·29)	7·59 (2·26)	$p < 0·001$ (n=27)	7·91 (2·36)	7·33 (2·26)	$p < 0·001$ (n=24)	8·19 (2·15)	7·93 (2·36)	NS (n=24)

Values for cardiac output (litres per minute) mean (SD); DA, donor atrial pacing; D-V, donor atrial-ventricular sequential pacing; mean, mean for all patients for all pacing rates; RV, right ventricular pacing.

Table 2 Comparison of donor atrial pacing with synchronous recipient-donor atrial pacing alone, and with sequential ventricular pacing

	DA	*RDA*		*D-V*	*RD-V*	
Pacing rate						
90/min	8·15 (1·38)	8·53 (1·62)	NS (n=4)	7·54 (1·54)	7·79 (1·52)	NS (n=2)
110/min	9·06 (1·60)	8·98 (1·26)	NS (n=6)	9·10 (1·64)	9·37 (1·35)	NS (n=5)
130/min	10·87 (1·81)	10·46 (1·50)	NS (n=6)	10·80 (2·40)	10·75 (1·99)	NS (n=4)
Mean	9·40 (1·96)	9·32 (1·64)	NS (n=16)	9·43 (2·14)	9·58 (1·84)	NS (n=11)

Footnotes as for table 1.
RDA, recipient-donor synchronous atrial pacing; RD-V, recipient-donor synchronous atrial-ventricular sequential pacing.

SYNCHRONOUS RECIPIENT-DONOR ATRIAL PACING

As mentioned already, to obviate any statistical problems associated with small numbers we have averaged the results in each mode of pacing. Despite this, there was no difference between donor and recipient-donor modes of pacing in our patients (table 2).

SYNCHRONOUS RECIPIENT-DONOR ATRIAL AV SEQUENTIAL PACING

As with atrial pacing, there was no statistical difference between conventional AV sequential pacing and synchronous recipient-donor atrial AV sequential pacing (table 2).

Discussion

We have shown that physiological pacing is indeed better than ventricular pacing alone in cardiac transplant recipients. Our data agree with those of an invasive study by Midei *et al* who reported a 19% mean improvement in cardiac output with atrial pacing at a single rate in nine patients.[15] Our theoretical supposition that the benefit of physiological pacing would not be as great as in native hearts is supported to some degree by the percentage benefit seen in our patients compared with the benefit reported in patients with native hearts. In our study conventional AV sequential pacing improved cardiac output by 8% overall compared with ventricular pacing; in native hearts, a similar study reported a benefit of 27% at a paced rate of 70 per minute.[4] Possible reasons for this lower benefit in cardiac transplant recipients include asynergy of recipient and donor atrial segments, but we were unable to show a benefit from synchronous electrical activation of the two atrial segments in terms of cardiac output at rest at the pacing rates studied. Denervation of the transplanted heart is unlikely to result in a decreased force of contraction of the donor atrium as the absence of parasympathetic stimulation should relieve the atrium of its normally negatively inotropic effects.[16] Another possible cause may be damage to the atrium during surgery, or distortion of the donor atrium after surgery resulting in incoordination of donor atrial contraction.

Why did electrical synchrony of recipient and donor atria not produce a benefit? In our apparently healthy cardiac transplant recipients it is possible that atrial synchrony was unnecessary to achieve maximal cardiac output at rest. After episodes of acute rejection, however, when left ventricular compliance may be reduced, a stronger active atrial component to left ventricular filling may become vital to preserve left ventricular function. The function of atrial contraction in normal subjects is to enhance ventricular filling above that which is possible by passive filling alone at normal mean atrial pressures. To preserve ventricular filling in the absence of atrial contraction, atrial pressure during diastole must therefore be higher than in a heart with normal anatomy. A decrease in left ventricular compliance will necessitate a further rise in mean atrial pressure which may precipitate pulmonary oedema. Thus electrical synchrony may be a prophylactic measure to avoid this sequence of events which may occur during rejection—either acutely or chronically.

We readily acknowledge that the numbers in our study are small, in particular those patients in whom recipient-donor atrial pacing was possible. Even summation of our data at all pacing rates in each mode to enable statistical comparison of larger numbers, however, did not suggest that an important benefit exists overall in transplant recipients from synchronous recipient-donor atrial pacing. We therefore stopped further enrolment in this study.

The cardiac output values found seem high when compared with reported cardiac output values from normal subjects at rest. The basal cardiac outputs in this study were only slightly higher and did not differ significantly from that seen in a previous study of cardiac transplant patients performed here.[17] A possible explanation for the high cardiac outputs seen in our study, however, is that all patients were within 21 days of major surgery and thus likely to be still in a hypermetabolic state. Another explanation might be that many of our patients were large in physical size (with body surface areas in excess of 2 sq m), and perhaps cardiac index would be more appropriate for absolute values. Our main objective in this study was not to provide absolute values for cardiac output in transplant recipients, but rather to emphasise the difference seen in cardiac output with different pacing modes.

Our study was performed at rest, and our results may not necessarily correlate with differences in cardiac output found during exercise at the pacing rates studied in the various pacing modes. We have no reason to suppose that there would be more benefit from ventricular pacing during exercise than with atrial pacing. Likewise, exercise is unlikely to result in any major haemodynamic change such that synchrony of recipient and donor atria would be significantly better.

Chronotropic competence during exercise may be beneficial in the transplanted heart, however, as the chronotropic response to exercise is abnormal in all cardiac transplant recipients.[18 19] Electrical connection of the atria would bring the donor under the control of the recipient sinus node (at least at heart rates above the basal tachycardia seen in transplant recipients) and the rate response to exercise would be preserved. Whether this would achieve an improved exercise capacity after cardiac transplantation deserves further investigation. Osterholtzer *et al*[12] report a 23 year old patient in whom sinus bradycardia after transplantation required pacemaker implantation. They describe the insertion of a dual chamber system with leads to recipient atrium (for sensing) and donor atrium (for sequential pacing). By setting the lowest delay (65 ms) they achieved physiological rate control using the recipient sinus node—"the most physiologic and best possible sensor".[12] They do not present any haemodynamic data, however, and thus no conclusion can be drawn as far as any benefit from relative synchronism of contraction is concerned.

In conclusion, physiological pacing is better than ventricular pacing after transplantation. Synchronous donor-recipient atrial pacing confers no additional benefit at rest in these patients. Whether it confers a chronotropic advantage remains to be determined.

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Arrhythmias after the Fontan procedure

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Abstract

Objective—To study the determinants and outcome of arrhythmias after the Fontan type operation.

Design—Retrospective analysis of data in patients operated on between 1972 and 1986 (follow up 5–19 years (mean 12 years)).

Patients—All 60 patients undergoing a Fontan type procedure at the National Heart Hospital, London, during the study period (mean age (SD) 12·3 (6·8) years).

Results—Postoperative arrhythmias occurred in 34 patients (57%), and 11 (58%) of 19 early postoperative deaths (within seven days) were related to arrhythmias. Early arrhythmias occurred in 19 (32%) patients of whom 11 (58%) died. All patients with early atrial fibrillation and His bundle tachycardia died and only preoperative atrial fibrillation recurred early. There was a higher incidence of early arrhythmias, which were less well tolerated, in double inlet single ventricle patients (9/19) than in those with tricuspid atresia (8/37). There were no other preoperative determinants of early arrhythmias or deaths from early arrhythmia. Late (after seven days) arrhythmias occurred in 15 (37% of hospital survivors). They had higher right atrial (RA) pressures both early and late after operation and had lower ventricular ejection fractions late after operation. Of those with atrial arrhythmias 86% had RA obstruction and 57% had an RA thrombus or pulmonary embolism at presentation; this was also confirmed in two patients in whom late sudden deaths occurred. Atrial fibrillation early after reoperation for RA obstruction was fatal. The actuarial arrhythmia free survival for hospital survivors was 60% at 10 years.

Conclusions—Early postoperative arrhythmias were poorly tolerated, particularly atrial fibrillation and His bundle tachycardia. Previous atrial fibrillation was a relative contraindication to this procedure. Late postoperative arrhythmias were associated with higher RA pressures measured both early and late after operation and worse late ventricular function. Late arrhythmias may be the first manifestation of RA obstruction, which must be sought. RA thrombus was common in patients with atrial arrhythmias and should be treated early with anticoagulants.

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After Fontan and Baudet's description of a procedure for functional correction of tricuspid atresia in 1971,[1] variations of the technique have been used for many complex anomalies including double inlet ventricle.[2] Arrhythmias cause problems in the natural history of these lesions but after creation of the Fontan circulation arrhythmias remain a risk and may be disastrous. This report focuses on the arrhythmias after the Fontan type operation and examines determinants of occurrence and outcome.

Patients and Methods

PATIENT SELECTION

Between 1972 and 1986 60 (31 male and 29 female) patients had a Fontan procedure, or a modification, at the National Heart Hospital London and all continued regular out patient attendance, providing at least five years of follow up in each case.

ASSESSMENT OF PATIENTS

Every patient had full preoperative clinical assessment including electrocardiography, echocardiography, cardiac catheterisation, and (since 1980) radionuclide ejection fraction assessment of the systemic ventricle. On completion of the Fontan procedure, right atrial pressure was measured before closure of the chest and continuously monitored for the first 24 hours through a central venous line, with continuous monitoring of cardiac rhythm during the operative and early postoperative period. During follow up, electrocardiography was carried out at six monthly clinic visits, with annual 24 hour Holter recordings, echocardiography, exercise testing, and radionuclide ejection fraction assessment. Invasive and other investigations were undertaken when clinically indicated.

In this study the early postoperative period was defined as the first seven days after operation. The occurrence of arrhythmias early and late (more than seven days) after the Fontan procedure was correlated with the following variables:

Preoperative—Underlying anatomical anomaly, previous shunt surgery, haemoglobin concentration, arrhythmias, ventricular function, left atrioventricular (AV) valve function, right atrial and pulmonary artery pressures, age at operation, and year of operation.

Postoperative—Immediate postoperative right atrial pressure, cardiac catheterisation pressure data, ventricular function, and age at onset of the arrhythmia.

STATISTICAL ANALYSIS

All group data are summarised as means (SD). Means were compared by unpaired Student's *t* tests. Differences in proportions were analysed with the Fisher exact test. Statistical significance was defined as $p < 0{\cdot}05$.

Table 1 Age at operation

Age group		*No of patients*
11 months	– 5 y	6
5 y	–10 y	18
10 y	–20 y	23
20 y	–28 y	13

Results

PATIENT POPULATION

The anatomical anomalies for which the 60 patients were undergoing surgery were tricuspid atresia (TA, 37 patients), double inlet single ventricle (SV, 19 patients), congenitally corrected transposition of the great arteries (TGA) with absent venous atrioventricular (mitral) connection (two patients), double outlet right ventricle with straddling tricuspid valve, TGA and pulmonary valve stenosis (one patient), and pulmonary atresia with intact septum (one patient). Ages at operation ranged from 11 months to 28 years (mean 12·3 (6·8) years) (table 1). Previous shunt procedures had been performed in 44 patients (systemic to pulmonary shunt in 39, Glenn anastomosis in nine, both in four), the first of which was between two and 27 (mean 11 (4·6)) years before the Fontan procedure. Seven patients had a functional Glenn anastomosis after the Fontan procedure.

SURGICAL PROCEDURE

Figure 1 shows the chronological distribution of the 60 procedures during the period covered by our study. Various surgical techniques resembling the procedure first described by Fontan[1] were used, some of which are now performed only infrequently at most centres. The right atrium was connected to the main pulmonary artery either by direct anastomosis (six patients) or through a conduit (35 patients, 32 with aortic homograft conduits and three with Dacron), to a mobilised subvalvar pulmonary outflow with a conduit incorporating the native pulmonary valve (five patients), and to the right ventricular infundibulum (14 patients).

POSTOPERATIVE FOLLOW UP

Postoperative follow up was five—19 (mean 12·0 (4·2)) years.

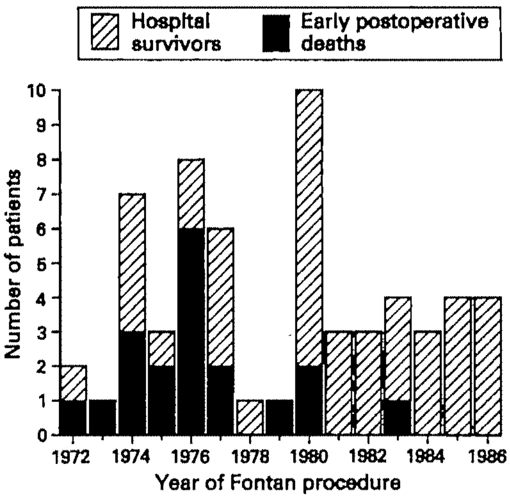

Figure 1 Distribution of Fontan procedures 1972–86, and hospital mortality.

Early deaths occurred in 19 patients (32%); 16 of 29 (55%) before 1980 and three of 31 (10%) thereafter. This lessening of mortality was attributable to stricter patient selection and improved surgical technique.

Postoperative arrhythmias were documented in 34 patients (57%)—19 early and 15 late (four with both an early and a separate late presentation and nine within 24 hours after reoperation).

Eleven (58%) of the 19 early deaths in hospital throughout the 15 year study period were directly associated with the onset of an arrhythmia.

EARLY ARRHYTHMIAS

Table 2 summarises the arrhythmias found and their outcome in the early postoperative period; 19 patients (32%) had early arrhythmias and of these 11 (58%) died in this period. Atrial fibrillation (five patients) and His bundle tachycardia (two patients) were always fatal. Four of the patients had an arrhythmia documented before the Fontan procedure (atrial fibrillation in one, reentrant supraventricular tachycardia in two, and an accelerated atrioventricular junctional rhythm in one), but only atrial fibrillation recurred in the early postoperative period, causing a rapid and uncontrollable ventricular response rate that led to death. The incidence of early arrhythmias was higher in SV (9/19 (47%)) than TA (8/37 (22%)) ($p = 0{\cdot}048$), although the types of rhythm disturbance were the same in both groups. Early arrhythmias in the SV group were less well tolerated; 37% of patients

Table 2 Early postoperative arrhythmias (19 patients)

	Rhythm																		
	NR (n=5)					*AF (n=6)*						*AFlut (n=3)*			*HBT (n=2)*		*VT (n=2)*		*CHB (n=2)*
Anomaly	SV	TA	TA	SV	SV	SV	SV	TA	TA	SV	TA	DORV	TA	PA	SV	TA	SV	SV	SV	TA
Age at operation (yr)	21	25	8	10	11	1	22	15	1	3	17	5	18	12	14	6	21	15	21	7
Fatal	0	0	0	+	+	+	+	+	+	+	+	0	0	0	+	+	0	+	0	0

NR, nodal rhythm (rate <130 beats/min); AF, atrial fibrillation; AFlut, atrial flutter; HBT, His bundle tachycardia; VT, ventricular tachycardia; CHB, complete heart block; SV, double inlet single ventricle; TA, tricuspid atresia; DORV, double outlet right ventricle; PA, pulmonary atresia with intact ventricular septum; +, death associated with arrhythmia; 0, survivor.

Table 3 Late postoperative arrhythmias (15 patients)

	Rhythm																
	NR (n=3)			*AF (n=3)*			*AFlut (n=4)*				*SVT (n=3)*			*VT (n=2)*		*New CHB (n=1)*
Anomaly	TA	SV	TA	SV	SV	TA	TA	TA	SV	TA	TA	TA	PA	TA	SV	TA
Age at operation (yr)	8	24	18	20	14	11	5	12	23	7	11	12	12	12	21	8
Age at arrhythmia (yr)	9	25	19	30	22	12	6	13	25	16	20	20	13	19	22	15
RA-PA obstruction	0	0	0	+	+	0	+	+	+	+	0	0	0	+	0	0

Footnotes as for table 2 except +, right atrial to pulmonary artery obstruction; 0, no obstruction.

operated on for SV died with early arrhythmias as compared with 11% in the TA group (p = 0·033). Complete atrioventricular block appeared in two patients with TA and was well tolerated; both had permanent epicardial pacing systems implanted later. An early arrhythmia was documented in the patient with pulmonary atresia (atrial flutter) and the patient with double outlet right ventricle (atrial flutter).

When the preoperative variables of patients with early postoperative arrhythmias were compared with patients without arrhythmias, there were no significant differences in age (mean 12·2 (7·3) *v* 13·2 (6·9) years), right atrial pressure (mean 6·0 (2·9) *v* 5·9 (2·1) mm Hg), pulmonary artery pressure (mean 12·6 (4·4) *v* 15·4 (5·6) mm Hg), previous shunt duration (mean 11·7 (4·8) *v* 10·9 (3·9) years), ventricular function, or the presence of atrioventricular valve dysfunction.

Although not reaching statistical significance, there was a trend to higher right atrial pressures in the first 24 hours after operation in those patients with early postoperative atrial fibrillation (mean 16·7 (2·9) mm Hg) than in those either with or without other arrhythmias (15·4 (3·4) mm Hg and 14·2 (3·1) mm Hg respectively.

Preoperative characteristics in the group with fatal early arrhythmia were not significantly different from those in the survivors of an early arrhythmia or in the non-arrhythmic group.

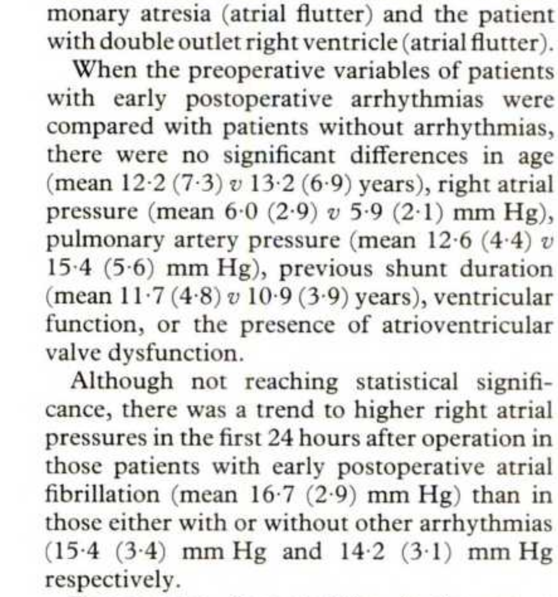

Figure 2 Magnetic resonance gradient echo image in the transverse thoracic plane (caudocranial view) at the level of the mid right atrium in end systole. This image shows blood (b) as a strong signal (white) and thrombus (t) as an attenuated signal (grey/black) in the right atrium. This thrombus was not seen on single plane angiography.

LATE ARRHYTHMIAS

Table 3 summarises arrhythmias and their outcome in the late postoperative period. Comparison of the preoperative variables in patients with and without late postoperative arrhythmias showed no significant differences in age at operation (mean 13·7 (6·0) *v* 13·2 (6·9) years), underlying anomaly, presence of preoperative arrhythmia, right atrial pressures (mean 6·8 (2·8) *v* 5·9 (2·1) mm Hg), pulmonary artery pressures (mean 12·8 (4·2) *v* 15·4 (5·6) mm Hg), previous shunt surgery, and ventricular or AV valve function. There were no apparent preoperative determinants of those who were to develop rhythm disturbances late after the first Fontan procedure.

At cardiac catheterisation, however, between one and eight years after the Fontan procedure, pressures were higher in patients who subsequently developed arrhythmias than those who did not, in both the right atrium (16·6 (4·9) *v* 11·3 (3·1) mm Hg); p = 0·008) and pulmonary artery (12·4 (2·5) *v* 8·9 (3·1) mm Hg; p = 0·013). The seven patients who developed atrial fibrillation and flutter tended to have the highest right atrial pressures (mean 17·5 mm Hg) before the start of the arrhythmia and after restoration of sinus rhythm, and six of these patients had a gradient between the right atrium and pulmonary artery of 5 mm Hg or more, confirming significant obstruction to right atrial outflow that was clinically apparent in only two cases. Patients who developed late arrhythmias after the Fontan procedure had significantly higher mean right atrial pressure as early as 24 hours after the procedure than those who did not (mean 18·2 (3·3) *v* 14·5 (3·7) mm Hg; p = 0·010).

Ventricular function (as determined by radionuclide ejection fraction), of patients when in sinus rhythm within two months of the onset of an arrhythmia was worse than in non-arrhythmic patients (mean ejection fraction 35% (11·9%) *v* 45% (10·4%); p = 0·034), measured in both groups at a mean of five years after the Fontan procedure. The mean preoperative ejection fraction for both these groups was 52% (11·5%).

Of the 15 patients with late arrhythmias two (sinus bradycardia with atrioventricular nodal escape rhythm one, atrial fibrillation one) were asymptomatic, nine (atrial flutter four, atrial fibrillation two, AV reentrant tachycardia two,

Table 4 Early arrhythmias after reoperation (in nine of 18 patients)

	Rhythm								
	NR (n=1)	*AF (n=3)*			*AFlut (n=2)*		*SVT (n=1)*	*VT (n=1)*	*New CHB (n=1)*
Previous arrhythmia	AF	—	AF	AF	AF1	—	—	—	—
Age at reoperation (yr)	28	12	22	17	9	25	23	13	12
RA-PA obstruction	+	+	+	+	0	+	+	+	+
Fatal	0	+	+	+	0	+	+	+	+

Footnotes as for tables 2 and 3 as appropriate.

ventricular tachycardia one) experienced associated palpitation, two (atrial fibrillation one, ventricular tachycardia one) had angina-like chest pain, one (atrial flutter) had syncope, and one (atrial flutter) had haemodynamic collapse. After the onset of an arrhythmia exercise tolerance and ability index (as defined by Warnes and Somerville[3]) were reduced. The reduction persisted even after restoration of stable sinus rhythm. After the onset of arrhythmia, investigation showed a new thrombus in the right atrium in two patients and pulmonary embolism was suspected in two more; this was confirmed by perfusion scanning in one. All four of these patients had atrial fibrillation or flutter. A large right atrial thrombus that was missed at angiography was clearly shown on magnetic resonance imaging in one case (fig 2). Of the five late sudden deaths in this series, data from necropsy exists in three patients, showing pulmonary embolism in one and right atrial thrombus in another. Survivors of early postoperative arrhythmias were no more likely to develop late arrhythmias than patients who had no early arrhythmias.

REOPERATION

Reoperation for right atrium to pulmonary artery obstruction was carried out in 18 patients in this series, three months to 14 (mean 6·8 (3·7)) years after the first Fontan procedure. Of these, 15 had obstruction of right atrium to pulmonary artery flow with a gradient of at least 5 (mean 7·6 (2·4)) mm Hg. Early arrhythmias occurred after reoperation in nine (50%) of the reoperated patients. Three of these patients had atrial fibrillation early after reoperation, again with fatal outcome. Two of these three patients had had atrial fibrillation late after the original procedure (table 4).

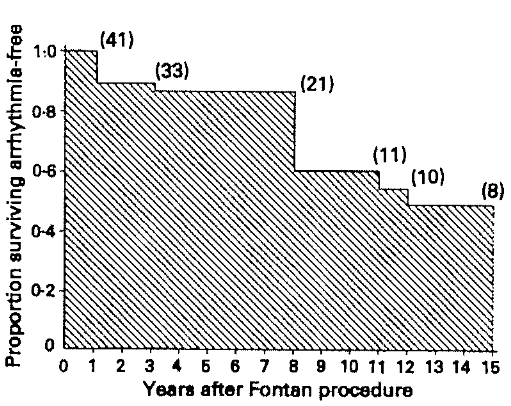

Figure 3 Arrhythmia free survival of the 41 hospital survivors of the Fontan procedure 1972–1986. This figure shows a probability of arrhythmia free survival of 60% at 10 years (11 patients) and 50% at 15 years (eight patients).

Figure 3 shows the actuarial arrhythmia free survival (AFS) curve for hospital survivors of the Fontan procedure (41 patients). Eleven patients remain free of arrhythmia at 10 years—an actuarial 10 year AFS of 60%. Eight patients remain free of arrhythmia at 15 years—an actuarial 15 year AFS of 50%.

Discussion

The long follow up in this series includes the pioneering experience of the Fontan procedure, with inevitable errors in patient selection as well as operative technique reflected in the higher mortality and morbidity before 1980.

The incidence of early postoperative arrhythmias was 32% (19/60 patients) with a fatal outcome in 58% (11/19 patients).

Atrial fibrillation occurred in the early postoperative period in 10% of patients, and was fatal in all cases probably because the importance of unfavourable factors which lead to a higher postoperative right atrial pressure had been underestimated. Atrial fibrillation was more common in double inlet ventricle than in tricuspid atresia even though age and preoperative pulmonary artery pressures were similar in the two groups. This probably relates to the more extensive atrial surgery in double inlet ventricle and a tendency to underestimate the degree of pulmonary vascular disease.

There was a trend to higher immediate postoperative right atrial pressures in those who developed early atrial fibrillation and this may reflect an underlying haemodynamic problem that worsened with the arrhythmia.

Preoperative atrial fibrillation recurred in the early postoperative period. With such problems resulting from atrial fibrillation in the early postoperative period, we now regard documented preoperative atrial fibrillation as a relative contraindication to the Fontan procedure particularly in the presence of other adverse factors. Atrial fibrillation early after reoperation for right atrium to pulmonary artery obstruction was also associated with fatal outcome and should therefore influence the assessment of reoperative risk. If atrial fibrillation does occur in the early postoperative period it requires immediate conversion rather than only attempts to slow the ventricular rate. The newer technique of total cavopulmonary anastomosis may avoid such difficulties with atrial fibrillation.[4]

Atrial flutter, by contrast, was better tolerated early after the Fontan operation, and easily reverted to sinus rhythm, either spontaneously or by early DC countershock. His bundle tachycardia occurred in only two and was fatal because it could not be slowed or terminated; this arrhythmia was not encountered after reoperation.

The data relating to early postoperative arrhythmias in this series contrast with two recent studies; Kurer *et al* reported early postoperative arrhythmias in 31 (93%) of 33 patients of mean age 4·6 years, but death occurred in only three (10%).[5] Gewillig *et al* reported a series of mean age 7·1 years, in which 11 (9%) of 104 patients developed early arrhythmias, and 10 (90%) died.[6] The great variation in reported figures for both incidence and resulting mortality may arise from the difference in age of the populations, which was considerably greater in our series (mean 12·3 years), different surgical techniques, and an apparent absence of atrial fibrillation in the entire period of postoperative study in the other series. Recent reports of the experience of the Mayo Clinic show hospital mortality (8% and 11·7%) after Fontan operations performed in the 1980s resembling that in our series (10%), but give little specific information about arrhythmia.[7 8]

Atrioventricular junctional rhythms and complete atrioventricular block were both well tolerated early and late after construction of the Fontan circulation, which clearly is not critically dependent on the coordinated atrial transport of sinus rhythm.

The onset of late atrial arrhythmias after the Fontan procedure was related to raised right atrial pressure as measured both early and late after the surgery. Atrial arrhythmias were often the first manifestation of significant right atrial to pulmonary artery obstruction. Higher right atrial pressures after the Fontan procedure may be caused by pulmonary vascular disease, obstruction to right atrial outflow, or impaired ventricular function. Finding higher right atrial pressures as early as 24 hours after surgery in the group that subsequently developed arrhythmias may be explained by any of these mechanisms. In some cases obstruction and an excessive pulmonary vascular resistance were excluded at cardiac catheterisation, suggesting impairment of ventricular function as a cause.

By contrast with the series from Weber *et al*[9] early postoperative arrhythmias did not predict the occurrence of late arrhythmia. Right atrial thrombus with or without pulmonary embolism was associated with the onset of late atrial fibrillation and flutter. Deteriorating right atrial function and flow from increasing obstruction before the start of the arrhythmia is probably the cause, but the precise mechanism cannot be determined with certainty.

Conventional transthoracic echocardiography should be useful in the detection of right atrial obstruction and intracardiac thrombus but often a poor echocardiographic window makes it difficult to image the anteriorly placed conduit particularly in older patients. Transoesophageal echocardiography (TOE) is reliable for the detection of obstruction[10] as is magnetic resonance imaging (MRI) with flow studies,[11] although problems with R wave gating may make it difficult to acquire clear images with MRI if the patient is in atrial fibrillation. Either TOE or MRI (or both) should be performed regularly in the follow up of any Fontan patient, particularly when arrhythmias occur. Early recognition of obstruction is essential if atrial and ventricular function are to be restored or maintained; arrhythmias may be a late (but still the first) clinical manifestation of such obstruction, which may go unrecognised for a long period. Arrthythmias also occur without obstruction but, whether or not there is obstruction, anticoagulation should be considered in view of the risk of right atrial thrombus.

The continued deterioration in ventricular function and symptoms after reversion to sinus rhythm suggests that such deterioration is related to the cause rather than to the effect of the arrhythmia. The decline in ventricular function was similar in patients with ventricular and supraventricular arrhythmias—so the mechanism of arrhythmogenesis in those with supraventricular arrhythmia may therefore have involved left atrial distension secondary to a rising ventricular end diastolic pressure and mitral regurgitation in some cases. It is tempting, however, to suggest that the apparent deterioration in ventricular function, often with a normal sized systemic ventricle, in this group of patients may be a result of impaired filling from obstructed pulmonary flow at the right atrial to pulmonary artery connection, leading to progressive diastolic ventricular dysfunction. Filling characteristics are an important determinant of ventricular function. In the context of the Fontan circulation, in which the precise mechanism of pulmonary flow has never been conclusively determined, conventional methods of assessment of the function of the ventricle in the presence of restricted inflow characteristics may be misleading. Perhaps this explains the poor outcome after surgical relief of chronic right atrium to pulmonary artery obstruction, with a systemic ventricle now unable to cope with restoration of normal flow. Certainly the importance of early diagnosis and relief of obstruction, with or without arrhythmias, cannot be overemphasised.

To date it must be concluded that with the Fontan circulation the start of arrhythmias, particularly atrial, signal a deterioration in function and must stimulate an early search for a remediable cause. Treatment of the arrhythmia alone is inadequate and if right atrial to pulmonary artery obstruction remains unrecognised it may result in irreversible cardiac dysfunction.

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Repeatability of measurements and sources of variability in tests of cardiovascular autonomic function

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Abstract

Objective—**To determine the repeatability and sources of variability of clinical tests of cardiovascular autonomic function.**

Design—**The commonly used electrocardiographic related tests of autonomic function were studied. Two repeat measurements of all tests were made on all subjects on four separate days over a four week period.**

Subjects—**Ten normal subjects with no known autonomic dysfunction were investigated.**

Main outcome measures—**These were deep breathing (subject seated and supine), Valsalva manoeuvre, standing up from lying position, and normal relaxed breathing (subject supine). During the tests the electrocardiogram and respiratory pattern were recorded by computer. Beat to beat RR intervals were measured automatically from the electrocardiogram, and from these the results of the tests were calculated.**

Results—**Variance analysis showed significant between subject variability for all tests ($p < 0.005$), but some tests showed a much smaller relative within subject variability than others. Average repeatability data (within subject SD) for each test were calculated, and included deep breathing sitting (max-min) RR (46 ms), Valsalva ratio (0·17), and lying to standing RR ratio (0·11). These compare with between subject SDs of 65 ms, 0·38, and 0·13 respectively, at mean values of 305 ms, 1·92, and 1·15 respectively. The data highlighted one subject with the poorest repeatability, whose electrocardiogram turned out on closer inspection to be under atrial rather than sinus control at times. Poor repeatability in the other subjects was related to variability in the respiratory pattern, and in the deep breathing test, repeat variability was significantly correlated ($r = 0.79$) with variability in the respiratory amplitude ($p < 0.05$).**

Conclusions—**Repeatability data should be available to each laboratory carrying out autonomic function tests. The data provided in this study could be used as a baseline. Poor repeatability highlights the need to re-examine the test procedures, or the test data from specific subjects. Variability of respiratory pattern is associated with poor repeatability, and so careful instructions on respiration should be given to each subject before the tests.**

(*Br Heart J* 1992;68:205–11)

The autonomic nervous system (ANS) controls many body functions and is essential for wellbeing. Impaired autonomic function is associated with clinical abnormalities which include postural hypotension, sleep apnoea, diarrhoea, urinary retention, and impotence.[1] Diabetic subjects in particular suffer from autonomic dysfunction, and it has been estimated that between 20% and 40% have some evidence of damage to the ANS.[2] Early evidence of autonomic dysfunction is often a reduced cardiovascular response to a stimulus.[3 4] Since this reduced response was first documented[5] a series of simple non-invasive tests have been developed that assess the response of the cardiovascular system to different stimuli. In general the test results enable subjects to be assigned to one of four broad clinical groups ranging from normal to severely impaired.[6] A finer quantitative assessment, however, is important for research and for assessing the likely prognosis of a patient.[7 8]

Many different stimuli have been used to provoke a cardiovascular response; the most common are deep breathing, the Valsalva manoeuvre, and moving from a lying to a standing position. In various centres the test procedures are carried out differently, in particular with reference to the subject's position and the duration of the stimulus. Table 1 documents the variation in reported test procedures.

Normal ranges for autonomic function tests have been documented,[9 15 17 19 22] and show an age related decline in variability of heart rate. A wide range of values can be expected for a population of normal subjects at a given age although the expected range for an individual subject is smaller than the range for the subject's age. This is important for any follow up studies in an individual subject, as the better the repeatability of measurements the more readily any significant change in a test result will be identified. Despite the wide use of the tests within the clinical environment,

Table 1 Variation in test procedures and calculated measurements

Reference	*Position of subject*	*Duration of test*	*Calculated result*	*Variable calculated*
Deep breathing:				
Clark and Mapstone[9]	Sitting	6 cycles	Mean 6 cycles	(max − min) HR
Dyrberg *et al*[10]	Supine	5 cycles	Mean 5 cycles	(max − min) HR
Ewing *et al*[11]	Supine, sitting, standing	1 min	Mean 1 min	SD RR, (max − min) HR, (max − min) RR, mean ΔRR, mean ΔRR^2
Ewing *et al*[6 12]	Sitting	6 cycles	Mean 3 cycles	(max − min)/HR
Masaoka *et al*[13]	Sitting	6 cycles		(max − min)/HR
Mustonen *et al*[14]	Sitting	6 cycles	1 cycle, Mean 6 cycles	(max − min)/HR, (max/min) RR
O'Brien *et al*[15]	Supine/ semirecumbent	1 cycle		(max − min)/HR SD HR, (max/min) HR
Smith and Smith[16]	Supine	5 cycles	Mean 5 cycles	(max − min)/RR
Smith[17]	Supine	1 cycle		(max/min)/RR
Sundkvist *et al*[18]	Supine	6 cycles	Mean 6 cycles	(max/min)/RR
Weiling *et al*[19]	Supine	6 cycles	Mean 6 cycles	(max − min)/HR
Valsalva manoeuvre:				
Baldwa and Ewing[20]	Sitting	15 s†	Mean 3 manoeuvres	TR, VR
Clark and Mapstone[9]	Sitting	15 s†	Mean 3 manoeuvres	VR
Dyrberg *et al*[10]	Sitting	15 s†	1 manoeuvre	VR
Ewing *et al*[6 12]	Sitting	15 s†	Mean 3 manoeuvres	VR
Levin[21]	Semirecumbent	10 s†	Higher of 2 manoeuvres	VR
Mustonen *et al*[14]	Sitting	15 s†		VR
O'Brien *et al*[15]	Supine/ semirecumbent	15 s†	1 manoeuvre	(max − min) HR, SD HR, VR
Smith and Smith[16]	Supine	10 s†	1 manoeuvre	VR
Smith[22]	Supine	10 s†	1 manoeuvre	VR
Lying to standing:				
Clark and Mapstone[9]	Lying/standing	40 beats*		30:15 ratio windowed
Dyrberg *et al*[10]	Lying/standing	2 min*		30:15 ratio
Ewing *et al*[6 12]	Lying/standing			30:15 ratio windowed
O'Brien *et al*[15]	Lying/standing	1 min*		(max − min) HR, SD HR, (max/min) HR
Weiling *et al*[19]	Lying/standing			max HR, min HR, 30:15 ratio, 30:15 ratio windowed
Normal breathing:				
Dyrberg *et al*[10]	Supine	150 RR		mean RR
	Supine	5 cycles	Mean 5 cycles	(max − min) HR
Ewing *et al*[11]	Supine, sitting, standing	5 min		SD RR, (max − min) HR, (max − min) RR, mean ΔRR, mean ΔRR^2
Murray *et al*[23]	Standing	5 min		SD RR
O'Brien *et al*[15]	Supine	60 s		(max − min) HR, SD HR, (max/min) HR
Smith and Smith[16]	Supine	255 RR		SD RR

*After standing.
†Duration of time pressure was maintained.
HR, heart rate; VR, Valsalva ratio; TR, tachycardia ratio.

only limited information is available on the repeatability of these tests in normal subjects. The repeatability data that are published tend to be presented in different ways, with either SD, range, or coefficient of variation (CV; SD/mean). Table 2 is a summary of the published repeatability data for normal subjects.

As the repeatability of tests in normal subjects is not comprehensively documented, and possible causes for the variability within subjects are rarely considered, the aims of the study were:

(*a*) To determine the repeatability of a number of electrocardiographically related autonomic function tests already published.

(*b*) To comment, from the results obtained, on which tests are more likely to lead to repeatable results in clinical use.

(*c*) To determine the causes of poor repeatability and make recommendations on the way the tests are performed.

Methods

SUBJECTS

Ten volunteer subjects (eight men) were enrolled in the study. All subjects were well and none had any known autonomic dysfunction or heart complaint. Their ages ranged from 23 to 44.

TEST PROCEDURES

All the measurements were made in the same room, which was maintained at a constant temperature. One operator made all the measurements on the subjects, who did not eat or drink in the hour preceding the tests. The following analogue data were collected simultaneously during each test. A computer based data aquisition system was used with sampling at 250 Hz. The subject's electrocardiogram was recorded with disposable electrocardiogram chest electrodes to ensure good quality signals, and from this the beat to beat RR intervals were calculated. The respiration pattern during each measurement was recorded using a two channel magnetometer system to give chest and abdominal movements.[25] From these a calibrated lung volume displacement signal was obtained by summing the two signals in a proportion determined before the test session. The timing of the main section of each test (for example, the beginning and end of

Table 2 *Published repeatability of measurements in normal subjects*

Reference	*No of subjects*	*repeat*	*Age (yr) range*	*Measurement*	*Mean (SD) (range)*	*SD (range)*	*CV (%) (range)*
Deep breathing:							
Ewing *et al*[12]	13	10		(max – min) HR	31 (min^{-1}) (SD 6)	4 (min^{-1}) (3–5)	— —
O'Brien *et al*[15]	6	5	20–35	(max – min) HR	— —	— —	16 (7–28)
				(max/min) RR	— —	— —	6 (2–9)
				SD HR	— —	— —	21 (13–34)
Smith[17]	20	2		(max/min) RR	— —	— —	8·9 —
Valsalva manoeuvre:							
Baldwa and Ewing[20]	12	10	20–41	VR	1·83 (0·37) (1·22–2·48)	— (0·06–0·31)	— —
Baldwa and Ewing[20]	7	5	52–66	VR	1·49 (0·18) (1·28–1·80)	— (0·08–0·16)	— —
Ewing *et al*[12]	19	5–10		VR	1·71 (0·35)	0·15 (0·06–0·34)	— —
Levin[21]	30	2		VR	— (1·38–2·90)	— —	— —
O'Brien *et al*[15]	6	5	20–35	VR	— —	— —	9 (4–16)
				(max – min) HR	— —	— —	17 (4–29)
				SD HR	— —	— —	21 (2–27)
Smith[22]	19	2		VR	— (1·23–2·78)	— —	15·4 —
Lying to standing:							
Ewing *et al*[24]	5	5	21–45	30:15 ratio	1·19 (1·04–1·34)	— —	5·3 —
Ewing *et al*[12]	18	5–10		30:15 ratio (windowed)	1·27 (0·08)	0·11 (0·06–0·20)	9 —
O'Brien *et al*[15]	6	5	20–35	30:15 ratio (windowed)	— —	— —	9 (4–16)
				(max-min) HR	— —	— —	26 (12–31)
				SD HR	— —	— —	24 (10–41)

HR, heart rate; CV, coefficient of variation; VR, Valsalva ratio.

the Valsalva manoeuvre) was recorded with a manually operated switch connected to an input channel.

Each measurement session was a fixed sequence: deep breathing test (subject seated), Valsalva manoeuvre (performed twice and the average taken, subject seated), normal relaxed breathing (subject supine), deep breathing test (subject supine), and lying to standing test. Subjects rested for five minutes supine after the second Valsalva manoeuvre and before the relaxed breathing test in the supine position. The complete sequence was repeated twice during each measurement session. All subjects repeated the session on four separate days over a four week period, giving eight repeat measurements for each test on each subject.

During the deep breathing test subjects breathed regularly at six respiration cycles per minute, with their breathing synchronised to a triangular waveform acting as a visual cue on a display screen. Six cycles (one minute) were collected. During the Valsalva manoeuvre subjects maintained a mouth pressure of 40 mm Hg (5·3 kPa) for 15 seconds by blowing into a manometer. In the lying to standing test subjects were asked to move from a supine position on a couch to a standing position as quickly as possible. During normal relaxed breathing the subjects were asked to lie quietly and breathe normally, and after the five minute rest period their electrocardiogram was recorded for one minute.

ANALYSIS OF TEST DATA

For the deep breathing test both maximum (max) and minimum (min) RR intervals were determined for each breathing cycle, and the difference (max-min) RR and ratio (max/min) RR calculated. After the RR intervals were converted to instantaneous heart rate (HR) the difference (max-min) HR was also calculated. From these variables the results for the first breathing cycle, the average of breathing cycles two to four, the SD of all RR intervals (SD RR), and beat to beat changes in RR intervals (SD ΔRR) were calculated. For each Valsalva manoeuvre the ratio of the longest RR interval after the end of the manoeuvre to the shortest RR interval during the manoeuvre was calculated. The Valsalva ratio (VR) was taken as the mean ratio from each pair of consecutive Valsalva manoeuvres. The 30:15 ratio is the ratio of the RR intervals following the 30th beat after standing to the RR interval following the 15th beat after standing. Due to the difficulty in defining exactly the point at which a subject is standing, a windowed 30:15 ratio was also determined (the windows being 10 beats centred on the 30th and 15th beats) to allow the use of the shortest and longest RR respectively. The SD RR and the SD ΔRR were also calculated for normal relaxed breathing. For each of the measurements made while the subjects were deep breathing, the mean and SD of the peak to peak change in respiration were determined from breathing cycles two to four.

Table 3 Repeatability of measurements obtained in our study

Test	*Mean*	*Between subject SD*	*Within subject SD*	*Ratio within/between subject SD*
Deep breathing sitting:				
(max − min) RR (ms)	305	65	46	0·71
(max − min) HR (min^{-1})	22·8	5·4	3·5	0·65
(max/min) RR 1st cycle	1·44	0·13	0·12	0·92
(max/min) RR	1·40	0·10	0·07	0·70
SD RR (ms)	117	25	16	0·64
SD ΔRR (ms)	77	23	15	0·65
Deep breathing supine:				
(max − min) RR (ms)	266	55	51	0·93
(max − min) HR (min^{-1})	16·8	3·9	3·2	0·82
(max/min) RR 1st cycle	1·34	0·09	0·12	1·33
(max/min) RR	1·31	0·07	0·06	0·86
SD RR (ms)	102	19	17	0·89
SD ΔRR (ms)	74	19	18	0·95
Valsalva manoeuvre:				
(max/min) RR (VR)	1·92	0·38	0·17	0·45
Lying to standing:				
30:15 ratio	1·15	0·13	0·11	0·85
30:15 ratio (windowed)	1·36	0·11	0·11	1·00
Relaxed breathing supine:				
SD RR (ms)	50	15	13	0·87
SD ΔRR (ms)	45	16	10	0·54

HR, heart rate; VR, Valsalva ratio.

STUDY ANALYSIS

Variability between subjects, between days, and between repeats on the same day was assessed with analysis of variance. The SDs expressing the variability of each measurement in each test were calculated to enable differences between repeatability in each subject to be examined. Also, the average repeatability for each test was determined. To examine for any possible relation between variability of respiration and variability of test results, the deep breathing test was investigated quantitatively. This test was selected because an approach to analysing the respiratory waveform was readily apparent—namely, variability of the peak to peak respiratory pattern. The respiration pattern at the end of the Valsalva manoeuvre was variable and less amenable to quantitative analysis. The repeatability data were normalised to the mean value calculated for each subject, and correlated with mean respiration amplitude and resting RR before the test.

Results

REPEATABILITY OF TESTS

Table 3 shows the repeatability of results obtained during this study. Variance analysis showed significant between subject variability for all test results ($p < 0{\cdot}005$). No significant variability occurred between the repeat measurements on different days or between repeats within the same measurement session for any test result. Some tests, however, showed a much smaller within subject variability to between subject variability ratio than others.

Figure 1 shows the within subject variability in each subject for the three most commonly used tests. A few individual results were within the borderline or abnormal ranges of Ewing's definitions.[6] Four of the results from deep breathing sitting were borderline, and one abnormal. These results occurred in three subjects, two of whom were the oldest in the study group. Only one of the 80 results

Figure 1 Results of three common autonomic function tests: A, deep breathing; B, Valsalva; and C, lying to standing, showing the mean and within subject variability (SD) for each of the 10 subjects. The dashed lines separate the normal range (above) from the abnormal range (below).[6] The deep breathing test has an additional borderline range.

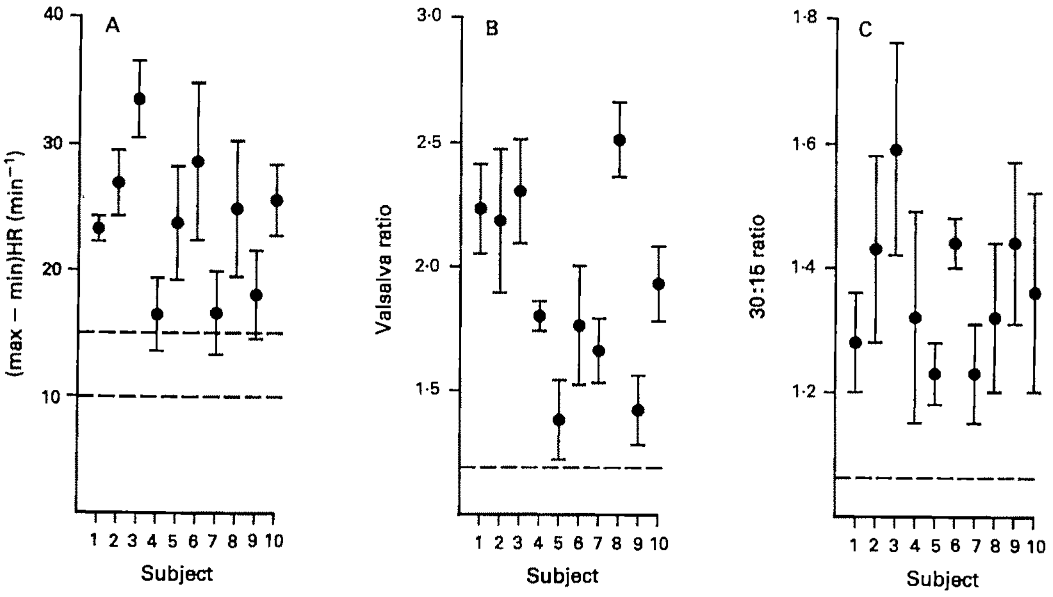
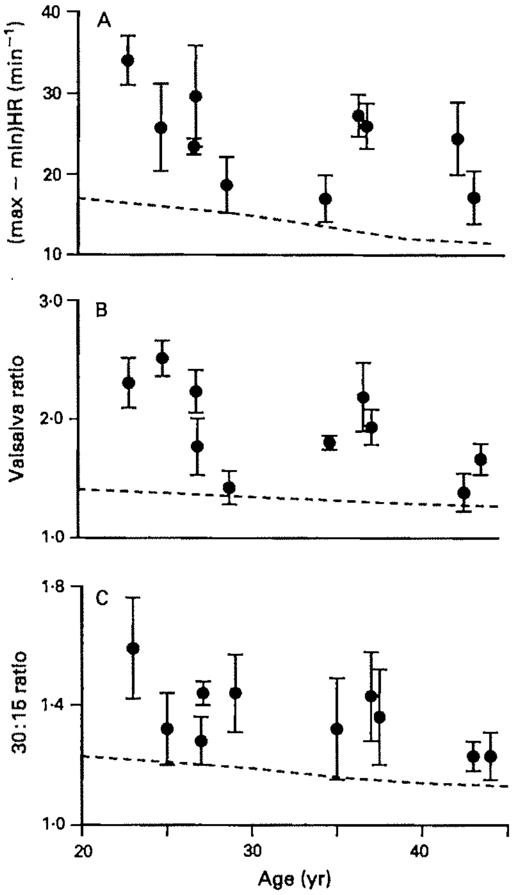


Figure 2 The results of this study: A, deep breathing; B, Valsalva; and C, lying to standing, fell within the normal range for the ages of the subjects. Dotted lines indicate the lower 90% confidence limits quoted.[6 15 19]



from the Valsalva ratio would be considered abnormal, and this occurred in one of the oldest subjects. All the windowed 30:15 ratios were above the lower limit of the normal range. When repeat measurements were taken into account, all mean results were within normal limits.

Figure 2 plots the results shown in figure 1 against age, confirming that the subjects fall within the normal age related ranges estimated by O'Brien *et al*[15] Ewing,[6] and Weiling *et al.*[19]

COMPARISON OF TESTS

Satisfactory tests, which readily distinguish between subjects, are those with a small within subject variability compared with between subject variability. To compare tests, table 3 provides the ratio of within subject SD to between subject SD. The smaller the ratio, the smaller the relative within subject variability and the better the test distinguishes between subjects. Clearly the Valsalva ratio fulfils this criterion the most satisfactorily. This is followed by SD ΔRR calculated from normal relaxed breathing. The variables calculated while deep breathing in the sitting position have a lower within subject variability compared with between subject variability than those calculated in the supine position. The mean results from three breathing cycles gave more repeatable results than those from a single cycle for the ratio (max/min) RR.

CAUSES OF POOR REPEATABILITY

When the data from all test procedures were plotted, the most striking qualitative finding was the relation between variability in respiration and variability of the test results. Figure 3 shows two examples from the deep breathing, Valsalva manoeuvre, and lying to standing tests. All clearly show how changes in the respiration pattern influence the results obtained. The pairs of examples for the deep breathing and the Valsalva manoeuvre shown were each taken from measurements on the same day for each subject. The magnetometer data were not normally recorded during the lying to standing test because of artifactual movement of the transducers during standing. Repeat recordings with the transducers fixed securely were obtained subsequently in one of the subjects.

The deep breathing test was selected for further quantitative analysis. For (max-min) RR in this test a relation between an increasing mean value and increasing SD was apparent for eight of the 10 subjects. When the SD/mean was calculated for each subject and compared with the SD alone, the range of the eight subjects (subjects 2–9) was reduced from 109% to 53%, and so this normalisation for the mean was undertaken before isolating other independent relations associated with increasing repeat variability.

The poor repeatability in one subject (subject 10) was found to be due to an intermittent change from an atrial to sinus rhythm with decreasing vagal tone on examination of the electrocardiogram. This subject was therefore excluded from further analysis of the causes of poorer repeatability.

For the relation between repeatability and variability of the way the test was performed, fig 4 illustrates how increased variability in test results is associated with increased variability of respiration ($r = 0{\cdot}79, n = 9, p < 0{\cdot}05$): there was also a trend in the relation with the mean resting RR preceding the test, but this was not statistically significant.

Discussion

A wide range of repeatability data for autonomic function tests in normal people is presented (table 3). Only a limited range of repeatability data has been published for autonomic function tests performed on the same occasion and repeated several times. Repeatability data are important because they provide information on quality control necessary for the effective running of a clinical laboratory testing autonomic function. The data provided here could be used as a baseline for such laboratories. It should be noted that different subjects can exhibit different levels of repeatability, and that different tests exhibit different repeatabilities. Such data are relevant when considering the follow up of individual subjects over an extended period.

The repeatability data presented in table 3 also allow comparison between tests and calculations made from these tests. The fact that all test measurements calculated show a significantly different (and lower) repeatability compared with the differences between subjects ($p < 0{\cdot}005$) confirms that all tests have value.

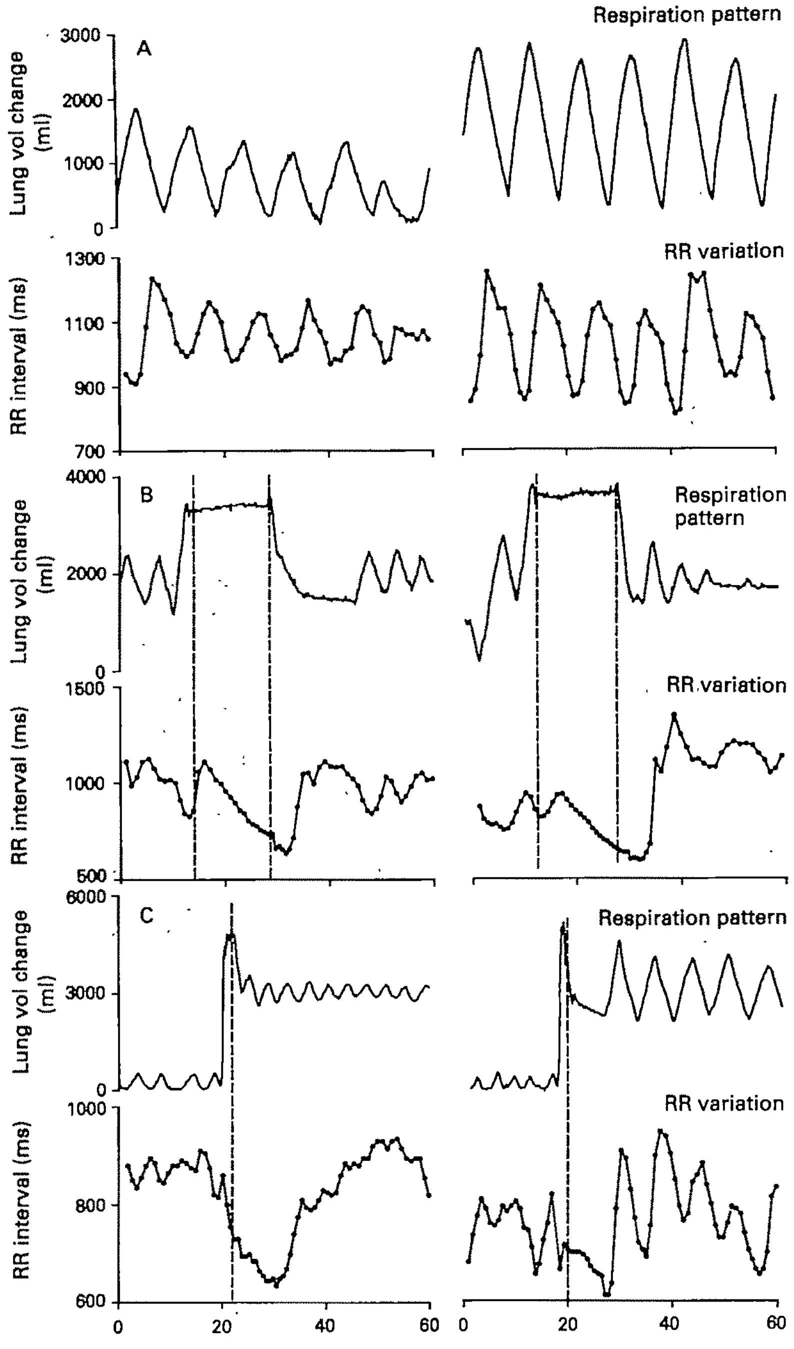


Figure 3 Examples illustrating how changes in respiration pattern alter RR variation and therefore the results obtained for: A, deep breathing; B, Valsalva; and C, lying to standing tests. Each pair of recordings is taken from the same subject.

The differences, however, were greater in some tests than in others. In particular, the Valsalva ratio stood out as having the lowest repeat variability. The other test with low repeat variability was the relaxed supine breathing test. This test is not usually included in the clinical battery of autonomic function tests,[6] but is easy to perform, with minimum instruction to the subject on how to breathe. During the deep breathing test, the sitting position gave more repeatable results for each variable than the supine position. This is perhaps because of the greater likelihood that subjects breathe more consistently with chest wall movement when sitting rather than with combined (and variable) chest and abdominal movements when supine. Also, as expected, averaging of three respiratory cycles was better than a single cycle measurement.

Even in this study, the repeatability data were valuable in identifying one subject with a heart rhythm that was not fully under vagal control. We were unaware of the atrial rhythm until the poor repeatability, combined with a consistent respiratory pattern, made us take a close look at the electrocardiogram, which had been stored in the computer during the test.

Our study shows that the greatest source of poor repeatability is variation in respiration. Better control of respiration during these tests should be advocated but we do not at this stage recommend respiratory monitoring, which is primarily a research technique. Instead, we suggest that more consistent instruction is given to the subject. For example, the subject could be asked to breathe shallowly after standing in the lying to standing test, or to refrain as much as possible from taking a particularly

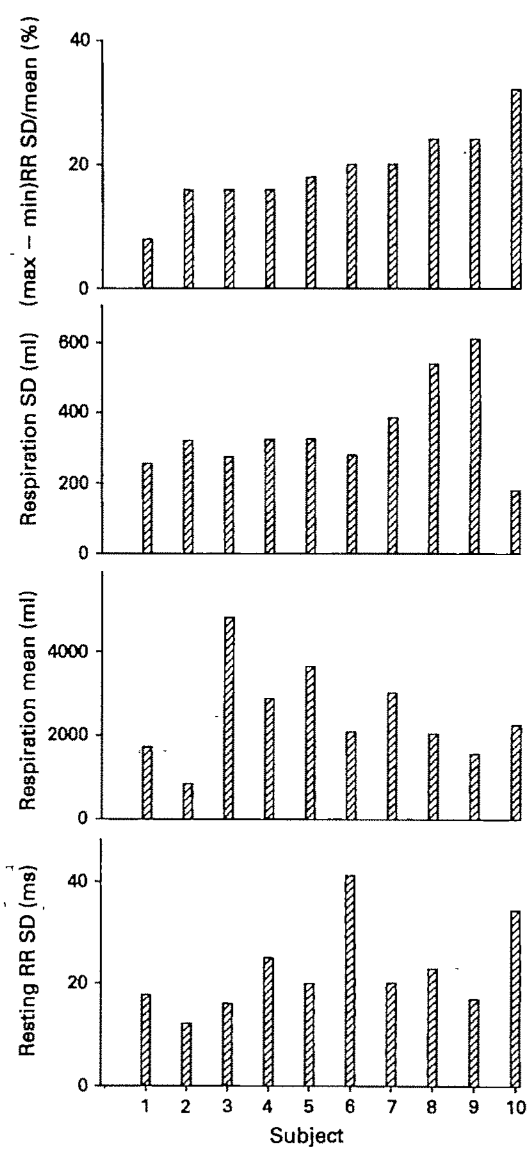


Figure 4 Repeatability of (max-min) RR, SD of respiration, mean of peak to peak respiration depth, and resting RR before the test.

large gasp after the Valsalva manoeuvre. Before the deep breathing test, subjects could be guided with a simple spirometer to breath a more consistent volume in a given time, and this volume could be noted for future tests.

Our study provides repeatability data in a consistent format for a wide range of autonomic function tests, enables repeatability of different tests to be compared, and documents the relation between repeatability and variability in respiration.

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Br Heart J 1992;68:212–3

Raised international normalised ratio (INR): Is it a cause or an effect of late cardiac tamponade?

P S Wong, W B Pugsley

Abstract

Two cases of late cardiac tamponade after valve replacement surgery are reported: both patients were treated with oral anticoagulants (warfarin) after operation. An erratic response in the international normalised ratio (INR) was found before the diagnosis of late tamponade. It is suggested that this response of the INR may be an early indicator of late cardiac tamponade rather than a cause.

(*Br Heart J* 1992;68:212–3)

Late cardiac tamponade is an infrequent but serious complication after cardiac surgery. The reported incidence is 0·1%–6%.[1-4] The overall mortality has been quoted as 18%.[5] Our report presents two patients with late cardiac tamponade who were found to have unforeseen increases in international normalised ratio (INR) while receiving warfarin after valve replacement surgery.

Case reports

A 63 year old man underwent insertion of a Starr-Edwards valve for severe aortic regurgitation. His postoperative recovery was uneventful. Warfarin treatment was started on the second day after operation. He was later transferred to his referral hospital on the seventh day after operation for further convalescence and was discharged home on the 10th day after stabilisation of his INR (between 2·0 and 3·5). He presented to his local hospital on the 26th day after operation with a 48 hour history of general malaise and worsening dyspnoea at rest. Two days before admission his INR had been 6·0 and his anticoagulation clinic reduced the dose of warfarin. The patient said that he had not taken medication other than that prescribed by the hospital. Examination of the patient showed signs of cardiac tamponade. The INR was 5·4 and liver function was mildly deranged. Other haematological and biochemical tests were unremarkable. The INR was partially corrected with a transfusion of fresh frozen plasma. Pericardiocentesis was performed after echocardiography had confirmed a large pericardial effusion. Eight hundred millilitres of heavily blood stained fluid was aspirated. The patient eventually recovered successfully.

A 59 year old woman underwent Starr-Edwards mitral valve replacement for mixed mitral valve disease. Her recovery after operation was excellent. Warfarin treatment was started on the day after surgery and she was transferred to her referral hospital on the sixth day after operation. She was discharged home three days later. She presented on the 18th day after operation with symptoms and signs of cardiac tamponade. There had been no change in her medication before admission except for a reduction in the dose of the warfarin as instructed by the anticoagulation clinic three days earlier. Her INR had then been 4·6 and despite a reduced warfarin dose was 9·0 on admission. This was partially corrected with a transfusion of fresh frozen plasma. A large pericardial effusion was confirmed by echocardiography, and pericardiocentesis was performed. Nine hundred millilitres of heavily blood stained fluid was aspirated. This resulted in considerable improvement of her haemodynamic state. She then recovered uneventfully.

Discussion

Late cardiac tamponade was first reported in 1968 by Prewitt *et al.*[3] It is defined as cardiac tamponade occurring seven days or more after operation. Most patients reported had had valvar surgery and nearly all were on anticoagulation treatment.[2 4-8]

The cause of late pericardial effusions is undoubtedly multifactorial. There is always a question of whether the anticoagulants could have triggered the start of late mediastinal haemorrhage, as most patients were receiving anticoagulants when cardiac tamponade occurred. Although no definite relation exists between anticoagulation and the occurrence of delayed cardiac tamponade, it has been suggested that excessive anticoagulation is a principal cause.[6 7] It is also possible that the retained mediastinal clot undergoes lysis with subsequent hydrophilic expansion causing cardiac compression.

In both the cases there was an erratic response of the INR to warfarin. Bashi *et al* and Hardesty *et al* have reported similar findings.[4 8] Bashi *et al* stated that patients with late cardiac tamponade maintained a high INR irrespective of whether they received a lower dose of warfarin or none at all.[4] The abnormal results of hepatic function tests, as evident in both our cases, suggest that this unpredictable response to warfarin reflects hepatic dysfunction, possibly as a result of cardiac compression.

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Any patient may take a drug that interacts with warfarin causing a rise in INR. Despite repeated warnings, patients occasionally take other drugs, even aspirin, without telling or consulting their doctors. In our two cases, however, there was no evidence of this.

Increased awareness and recognition of this insidious, but treatable complication should lower the high mortality associated with it. An unexpected prolongation of the INR response may be an early indicator of impending cardiac tamponade. We therefore suggest that this complication be considered whenever there is an erratic response to warfarin.

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Br Heart J 1992;**68**:214–5

CASE REPORTS

Rare variant of truncus arteriosus with intact ventricular septum and hypoplastic right ventricle

Benjamin Zeevi, Leslie Dembo, Michael Berant

Abstract

A three week old girl was admitted to hospital with severe congestive heart failure and cyanosis. Cross sectional and Doppler echocardiography and cardiac catheterisation showed a unique variant of truncus arteriosus with an intact ventricular septum. The trunk rose only from the left ventricle and was associated with a hypoplastic right ventricle with sinusoids to the right coronary artery.

(*Br Heart J* 1992;**68**:214–5)

Truncus arteriosus is defined as a single arterial trunk leaving the base of the heart via a single arterial valve to supply the systemic, pulmonary, and coronary circulations.[1] A truncus arteriosus with an intact ventricular septum is rare.[2] We describe a most unusual case of truncus arteriosus with intact ventricular septum and hypoplastic right ventricle with sinusoids.

Case report

A three week old girl was transferred to our hospital for cardiac evaluation. She was mildly cyanosed with a respiratory rate of 80 per minute and a pulse rate of 150 beats/minute. Blood pressure was 70/40 mm Hg with bounding peripheral pulses. Examination showed an active precordium with a loud systolic ejection click at the apex. The second heart sound was loud and single. A grade 3/6 ejection systolic murmur was best heard at the apex and the left sternal border. A 2/6 mid-diastolic murmur was best heard at the apex.

A chest *x* ray showed severe cardiomegaly with increased pulmonary vascular markings. An electrocardiogram showed right atrial enlargement, left ventricular hypertrophy, and diffuse ST-T segment depression.

Cross sectional and Doppler echocardiography showed situs solitus and normal systemic and pulmonary venous connections. The right atrium was very large with aneurysmal bulging of the interatrial septum into the left atrium. The tricuspid valve was hypoplastic but patent and opened into a hypoplastic muscular right ventricle with sinusoids (fig 1A). The mitral valve looked abnormal with moderate stenosis and insufficiency. The left ventricle was large with normal function and the interventricular septum seemed to bulge from right to left in systole. A single arterial trunk originated from the left ventricle: it supplied a left aortic arch, both pulmonary arteries, and the coronary arteries (figs 1B and C). The truncal valve was biscuspid.

Cardiac catheterisation (table) showed a right-to-left shunt at the atrial level. Oxygen saturation was identical in the left pulmonary artery and aorta. The filling pressure of both ventricles was increased. The right ventricular

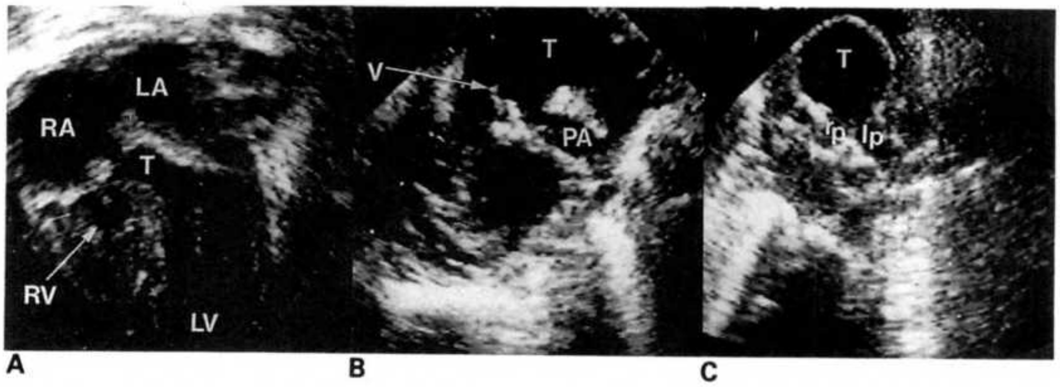

Figure 1 (A) Apical five chamber view showing the truncal root (in relation to the left ventricle) and a small hypertrophic right ventricle. (B) Parasagittal suprasternal view of the truncal arch: the pulmonary artery comes off its posterior aspect. (C) High short axis view of the truncus showing the origin of the pulmonary arteries. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; T, truncal outlet; V, truncal valve; PA, pulmonary artery; rp, right pulmonary artery; lp, left pulmonary artery.

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Data from cardiac catheterisation

Site	*Oxygen saturation (%)*	*Pressure (mm Hg)*
Superior vena cava	30	—
Right atrium	47	a = 28, v = 26, m = 18
Right ventricle	44	95/18
Left atrium	73	a = 20, v = 28, m = 18
Left ventricle	80	75/22
Aorta	73	60/40, m = 50
Left pulmonary artery	73	55/35, m = 45

pressure was suprasystemic and there was a 15 mm Hg peak systolic gradient across the truncal value.

CINEANGIOGRAMS

An anterograde injection of contrast into the root of the great artery, which arose from the left ventricle, showed that it supplied the left coronary artery, a left aortic arch, and both pulmonary arteries that rose from its posterior aspect (fig 2A). Though there was good opacification of the right cusp there was no filling of the right coronary artery. There was mild truncal regurgitation. A left ventriculogram showed large ventricle with normal function and mild mitral regurgitation. From this ventricle there was opacification of the truncal artery. A right ventriculogram showed a hypoplastic right ventricle with severe tricuspid regurgitation. From the right ventricle there was filling of multiple sinuoids with retrograde filling of the right coronary artery without opacification of the truncal root (fig 2B).

After the right ventriculogram was obtained severe bradycardia developed and progressed to complete atrioventricular block and hypotension. A rapid balloon atrial septostomy was performed and a temporary pacemaker was inserted but all attempts at resuscitation were unsuccessful.

On the basis of these data we diagnosed an unusual form of truncus arteriosus. The arterial trunk arose only from the left ventricle: the interventricular septum was intact, and the right ventricle was hypoplastic with multiple sinusoids and retrograde filling of the right coronary artery, which was probably atretic in its origin. There was mild stenosis and insufficiency of the truncal valve, an abnormal mitral valve, and aneurysm formation of the interatrial septum.

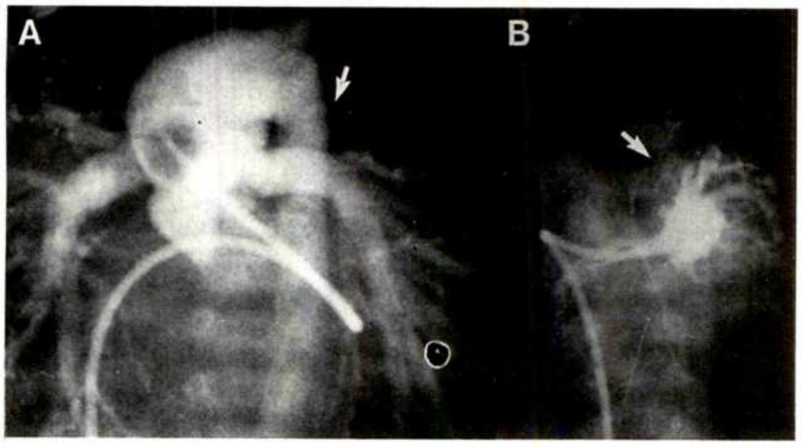

Figure 2 (A) Truncal root injection showing the anatomy of the root and the filling of the left coronary artery (arrow). (B) Right ventriculogram showing a severely hypoplastic right ventricle with multiple sinusoids and retrograde filling of the right coronary artery (arrow).

Discussion

The present case is unusual in many aspects and does not conform to the conventional classification of truncus arteriosus.[3,4] However, the definition of truncus arteriosus as a solitary arterial trunk guarded by a common arterial valve and directly suppling the coronary, pulmonary, and systemic circulations would include this unusual variant.[1]

The first unusual feature was the origin of the trunk entirely from the left ventricle. This is a rare anomaly found in only 4–6% of patients with truncus arteriosus.[3,5] In most patients the truncal valve overrides the ventricular septum and arises in approximately equal proportions from the right ventricle and the left ventricle.

The second distinctive feature was the absence of a ventricular septal defect. The ventricular septal defect in truncus arteriosus is generally large and results from either absence or pronounced deficiency of the infundibular septum.[6] Very rarely the ventricular septal defect in truncus arteriosus may be small and restrictive or even absent.[2]

The association of left ventricular origin of the truncus arteriosus and absence of a ventricular septal defect left the right ventricle without an outlet. This anatomical arrangement resembles that in cases of pulmonary valve atresia and intact ventricular septum with hypoplastic right ventricle. In our case, as in these cases,[7] there were multiple sinusoids that connected the right ventricular cavity to the coronary artery and functioned as the sole outlet for this ventricle. The origin of the right coronary artery from the truncus arteriosus was probably atretic because this vessel did not fill from the truncal root injection and there was no retrograde filling of the truncus arteriosus when the right coronary artery filled retrogradely during the right ventricular angiogram.

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Br Heart J 1992;68:216–7

Unmasking of a second atrioventricular accessory connection by adenosine in a child with a long RP′ reentrant tachycardia

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Abstract

A second unidirectional, retrograde accessory atrioventricular pathway was unmasked by adenosine during the intracardiac evaluation of a child with a reentrant long RP′ tachycardia. This case is further evidence of the value of adenosine during the evaluation of these types of tachycardias.

(*Br Heart J* 1992;68:216–7)

Adenosine generally terminates orthodromic supraventricular tachycardia through its anti-dromotropic effects on the anterograde limb (that is, the atrioventricular node) of reentrant atrioventricular tachycardias.[1-3] However, in patients with reentrant forms of long RP′ tachycardia, adenosine also has anti-dromotropic effects on the retrograde limb.[3 4] These anti-dromotropic effects occur because of the postulated "atrioventricular node like" properties of the retrograde limb. We report a case in which adenosine by producing transient retrograde conduction block unmasked a second unidirectional retrograde atrioventricular accessory pathway.

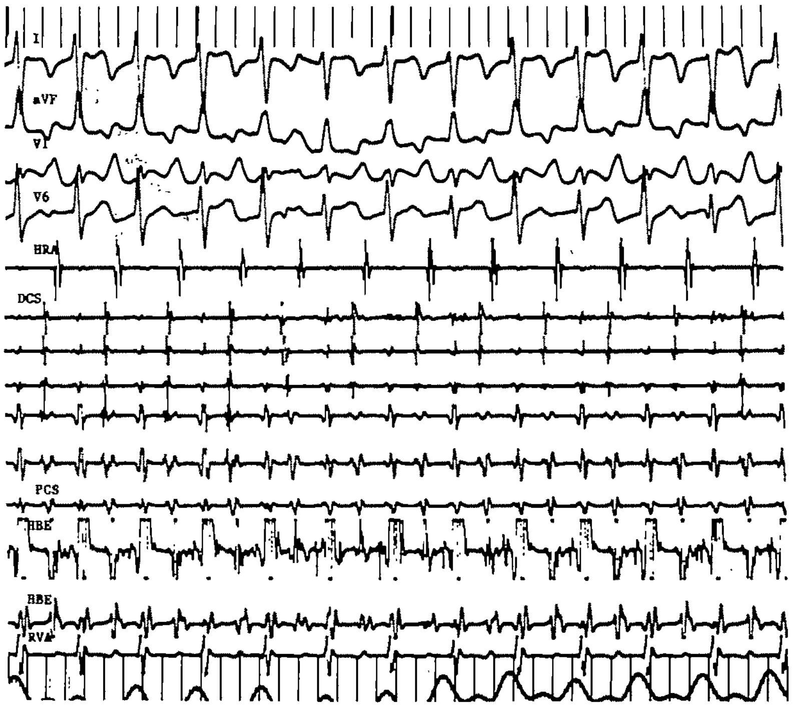

Figure 1 Surface electrocardiographic leads I, aVF, V1, and V6 recorded simultaneously with high right atrial, six coronary sinus, two His-bundle, and one right ventricular apex electrocardiograms after adenosine administration during tachycardia. The tachycardia cycle length is 320 ms. After the first four QRS complexes the site of earliest retrograde atrial activation was pair 4 of the coronary sinus (CS) catheter. After the fifth QRS complex the atrial activation sequence changed so that the distal CS pair was earliest. This second atrial activation sequence after transiant retrograde conduction block of the primary limb suggests a second retrograde pathway. HRA, High right atrial; DCS, distal coronary sinus; PCS, proximal coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

Case report

Intermittent tachycardia was first diagnosed in a four year old white girl six months before admission. She had been symptom free apart from a tendency to tire quickly with exercise. Her physical examination was remarkable only for the presence of an irregular heart rate. Her surface electrocardiogram showed long RP′ tachycardia with a heart rate of 165 beats per minute, an RP/RR ratio of 61%, and negative P waves in leads I-III and aVF. A 24 hour ambulatory monitor showed 22% tachycardia. Her chest *x* ray and echocardiogram were normal.

Because the tachycardia was resistant to digoxin, propranolol, and verapamil, an intracardiac electrophysiological evaluation with pre-ablation mapping was performed. This study included both atrial and ventricular protocols at rest and during autonomic blockade. No pre-excitation was noted during sinus or paced atrial rhythms. During ventricular (VOO) pacing, a unidirectional retrograde accessory pathway was mapped off the septum in the posterior wall of the left atrium. A retrograde Wenckebach block was elicited during VOO pacing at a cycle length of 290 ms, suggesting that this limb had decremental properties. By producing a transient retrograde conduction block, the administration of adenosine during tachycardia provided further evidence about the decremental properties of this pathway. Furthermore, during the single beat of retrograde conduction block produced by adenosine a second retrograde atrial activation sequence was unmasked (fig 1). This finding implied a second unidirectional retrograde pathway located in the lateral left atrium. After autonomic blockade, this unmasked retrograde atrial activation sequence was again noted when a retrograde block was produced by introducing single premature ventricular contractions into VOO pacing.

Because of these findings the patient had surgical ablation. Her intraoperative epicardial map confirmed both pathways (fig 2). The incision was extended well into the lateral free wall of her left atrium. Postoperational wire electrode studies showed the absence of

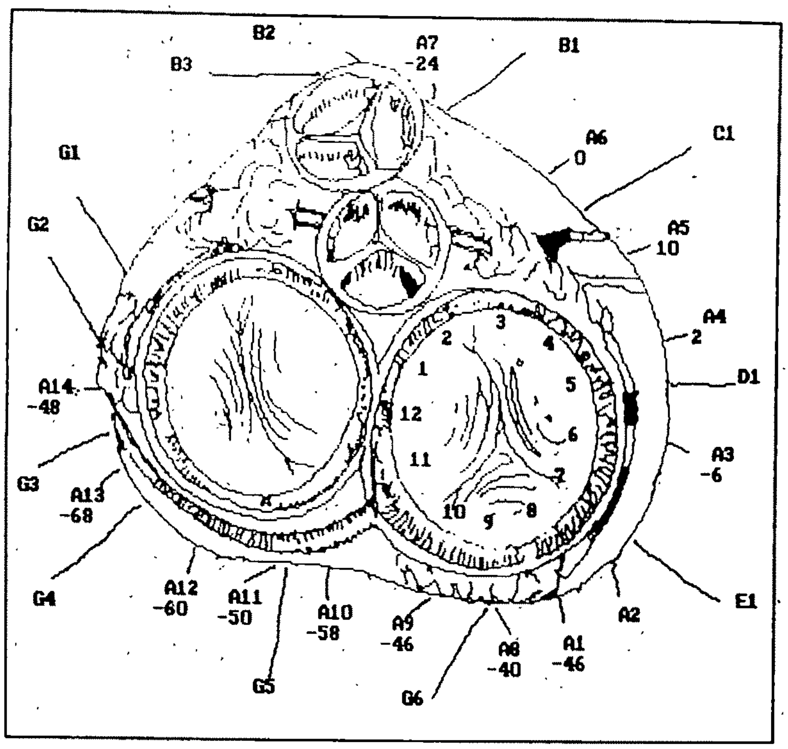

Figure 2 Intraoperative map during supraventricular tachycardia. The illustration is a cross section of the heart as viewed from above. The mitral valve is to the left, the tricuspid valve to the right, and the pulmonary valve most anterior. The letter-number combinations (for example, G4) represent specific mapping sites. The negative numbers represent atrial activation as referenced to a right atrial appendage electrogram. Therefore, the more negative the number the earlier the atrial activation sequence. There are two non-contiguous areas of early atrial activation: A13 (left lateral free wall) and A10 (left posterior free wall).

retrograde conduction. She has remained tachycardia free during four months of follow up.

Although the location of the retrograde limb of reentrant long RP′ tachycardias, and therefore the site of earliest retrograde atrial activation, may vary with the specific type of tachycardia (that is, "fast-slow" form of atrioventricular node reentrant tachycardia versus the permanent form of junctional reciprocating tachycardia versus accessory atrioventricular pathways well away from the septum), these limbs commonly have "atrioventricular node like" properties.[3 4] It is this characteristic that gives adenosine the ability to terminate tachycardia in either limb of these reentrant forms of tachycardia.

Because the conduction of the primary unidirectional retrograde limb of this child's tachycardia, had "atrioventricular node like" properties it was transiently blocked by adenosine. And this unmasked, a second unidirectional retrograde accessory atrioventricular pathway (fig 1). Although it is impossible to exclude a premature atrial contraction as the cause of this second atrial activation sequence, the reproducibility of this second activation sequence during catheterisation and the demonstration of two non-contiguous areas of early atrial activation on an intraoperative map are strong evidence of a second pathway.

Adenosine not only gave information about the decremental properties of the retrograde limb but helped to establish the presence of a second accessory pathway. The combination of these diagnoses was important when this child was assessed for surgical or radiofrequency catheter ablation. As has recently been reported by Bharati *et al* these pathways with "atrioventricular node like" properties may in fact be left sided atrioventricular nodes that may prove difficult to ablate by catheter techniques.[5] This factor, combined with evidence of a second pathway, led us to favour surgical ablation.

The usefulness of adenosine for the evaluation of patients with long RP′ reentrant tachycardias is becoming more apparent. Adenosine is not only a powerful therapeutic agent but also an important diagnostic tool.

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Br Heart J 1992;**68**:218–20

Propionibacterium acnes causing an aortic root abscess

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Abstract

A case of endocarditis caused by *Propionibacterium acnes* associated with an aortic root abscess is presented. This supports the current opinion that aortic root abscesses are not necessarily associated with microorganisms of high virulence.

(*Br Heart J* 1992;**68**:218–20)

Endocarditis caused by *Propionibacterium* is very rare despite the frequent presence of the bacterium in sebaceous glands and in the bypass filter during operation.[1] A case is presented in which endocarditis of a prosthetic aortic valve caused by *Propionibacterium* was associated with an aortic root abscess.

Case report

A 34 year old man was admitted after a cerebrovascular accident. At the age of 13 he had had rheumatic fever. In 1978 he had been admitted with pericarditis and at that time an aortic regurgitant murmur was heard. He had subsequently progressed well until 1986 when he noticed that he was short of breath on exertion and more tired than usual. On examination he had the signs of aortic regurgitation. Cardiac catheterisation showed severe aortic regurgitation, a normal aortic root, and a dilated ventricle with good function. He underwent aortic valve replacement with a Starr-Edwards prosthesis as the native valve showed the signs of rheumatic damage. He made a good recovery.

On 19 July 1989 he was admitted to hospital with numbness and weakness in his right arm and leg which had come on suddenly. He was smoking 10 cigarettes a day and taking warfarin. On examination he looked well and was apyrexial. Auscultation of his heart showed only the signs of a normally functioning aortic valve prosthesis. He had mild expressive dysphasia and decreased sensation over the right side of his face, right arm, and right leg. Muscle power in all muscle groups of the right arm and leg was decreased, and the tendon reflexes were all brisk, and the right plantar response was upgoing. His international normalised ratio was 2·4, haemoglobin 14·1 g/l, white cell count 15·7 × 10^9/l, and erythrocyte sedimentation rate 27 mm/h. A computerised tomographic scan of his brain showed a haemorrhage in the left occipital region surrounded by oedema (fig 1).

Blood cultures were incubated for three weeks without terminal subculture. Two sets of blood cultures produced a growth of *Propionibacterium acnes* in the anaerobic bottles after six days of incubation. Another two sets yielded a similar organism after two weeks of incubation. A midstream urine culture was negative. The chest *x* ray film and an abdominal ultrasound showed no abnormalities. No complement fixing antibodies were detected for *Coxiella* species or *Chlamydia psittaci*. An autoantibody screen was negative.

The *Propionibacterium acnes* isolated was sensitive to penicillin, gentamicin, vancomycin, teicoplanin, and rifampicin. The minimum inhibitory concentrations were 0·03 mg/l, 1 mg/l, 0·25 mg/l, 0·06 mg/l, and 0·004 mg/l respectively. Minimum bactericidal concentrations were 0·12 mg/l, 16 mg/l, 0·5 mg/l, 0·25 mg/l, and 0·5 mg/l. The patient was treated with benzyl penicillin (2·4 g every four hours) and gentamicin was added when his fever failed to resolve within five days. The serum bactericidal dilution was 1/4 at peak and 1/2 at trough. His fever did not respond so antibiotic treatment was changed to vancomycin (1 g) and rifampicin (300 mg) twice daily giving a serum bactericidal dilution of 1/16 at peak and 1/8 at trough. His symptoms still did not improve, suggesting that a root abscess might be present. An early diastolic murmur was heard and echocardiography suggested the presence of an aortic abscess in showing thickening of the anterior wall of the aortic root and aortic regurgitation. Aortography confirmed an aortic root abscess

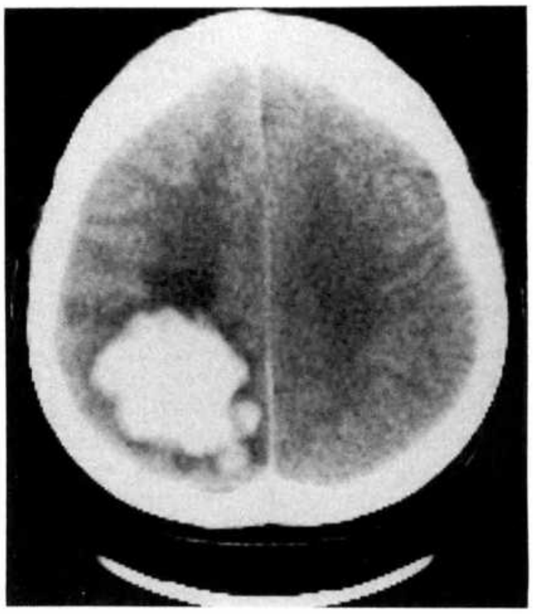

Figure 1 Computerised tomographic head scan showing a large occipital haemorrhage.

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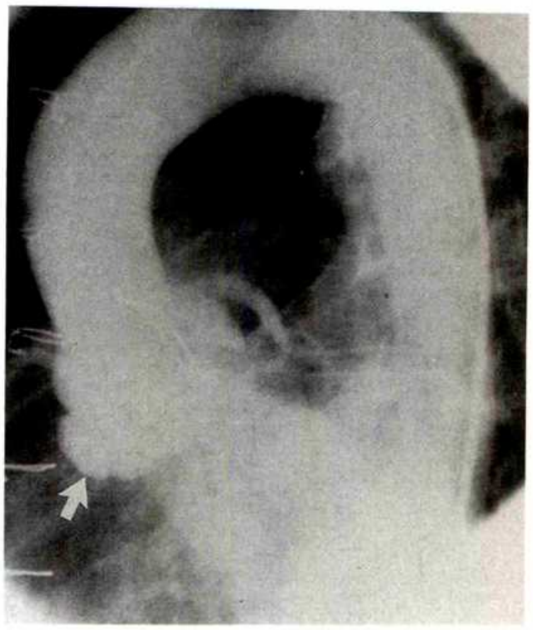

Figure 2 Aortogram showing an aortic root abscess.

(fig 2). The patient developed the "red man" response to vancomycin and the antibiotics were changed to teicoplanin (400 mg) once daily. But increasing pruritus forced a further change in antibiotic treatment to benzyl penicillin and gentamicin. In view of his recent intracerebral bleed, digital subtraction angiography of his cerebral arteries was undertaken and was normal.

He underwent replacement of the aortic valve and repair of an aortic root abscess; one suture caused complete heart block and was removed but first degree heart block developed on tightening the other sutures. After the operation he developed left bundle branch block and first degree heart block and thus a permanent pacing system was inserted. This was initially a VVI system but when he became dependent on the pacemaker he had symptoms of dyspnoea and tiredness so the pacemaker was replaced by a dual chamber system. This left him symptom free. He continued to receive benzyl penicillin for six weeks after surgery and he has made a complete recovery.

Discussion

Propionibacterium acnes is often considered to be a contaminant[2] but it has been found to be the principal pathogen in meningitis,[3] scalp pustules,[4] osteomyelitis,[5] central nervous system shunt infection,[6] endophthalmitis[7] and septic arthritis.[2] *Propionibacterium acnes* is also a rare cause of infective endocarditis.[8–10] It has been suggested that aortic root abscesses are caused by bacteria that are particularly virulent[11 12] although this is not borne out by later studies[13 14] or this case. *Propionibacterium acnes* is a slow growing anaerobic Gram positive coryneform. It has a pathogenic role in acne vulgaris and is found in sebaceous glands, thus cleaning the skin does not prevent operative contamination. Indeed *Propionibacterium* species can often be isolated from the blood of patients undergoing cardiopulmonary bypass who are given flucloxacillin and tobramycin prophylaxis (37%) but rarely from those receiving teicoplanin (2%).[1] It is thus surprising that infection by *Propionibacterium* species is so rarely documented and it has been suggested that this is due to the lack of good laboratory anaerobic conditions and prolonged culture.[8] *Propionibacterium acnes* is normally sensitive to penicillin, tetracycline, and teicoplanin.

In infective endocarditis, spread of infection to surrounding structures is more common with aortic valves. This may result in an aortic root abscess, annular erosion of the aortic root, mycotic aneurysm, or involvement of the aorticomitral apparatus. Aortic root abscess is more common with prosthetic valve endocarditis occurring in 52% compared with 15% of cases of native valve endocarditis.[13] Cross sectional echocardiography is helpful in identifying aortic root abscesses but few patients (< 5%) have the obvious finding of an echo free abscess cavity and thus the diagnosis rests on associated findings such as the wall of the aorta being more than 10 mm thick, prosthetic valve rocking, sinus of Valsalva aneurysm, or perivalvlar density in the septum of 14 mm or more. When these factors are considered, the positive and negative predictive values are 86% and 87% respectively.[15] Transoesophageal echocardiography is particularly helpful in diagnosing this complication of infective endocarditis[16] and magnetic resonance imaging may also clearly show an aortic root abscess.[17] The role of cardiac catheterisation in patients with infective endocarditis is debatable but most would advise its use before cardiac surgery[18–20] although the rationale for this, resting as it does upon diagnostic accuracy, is being constantly eroded as non-invasive diagnostic techniques improve. Interestingly cardiac catheterisation may be much safer than is often thought. In one study of 35 patients with infective endocarditis undergoing cardiac catheterisation there was not one embolic episode despite vegetations being seen echocardiographically on 15 of the 21 valves crossed by the catheter.[20] Similar experience has also been reported in another study.[21] We would not advocate crossing infected valves but think that aortography can be safely used in endocarditis of the aortic valve.

An aortic root abscess itself does not absolutely indicate the necessity for cardiac surgery,[13] and these abscesses have occasionally healed with medical treatment alone.[17] Some studies, however, show an improved survival rate with operative intervention in infective endocarditis in general especially when associated with a prosthetic valve.[18 22] If surgery is performed mortality is significantly higher in those with an aortic root abscess (13·6% compared with 2·2% for those without this complication).[13]

This case suggests that a blood culture growing *Propionibacterium acnes* should not be dismissed as a contaminant without first considering the clinical circumstances. In this patient *Propionibacterium acnes* caused an aortic root abscess. This supports the current opinion that an aortic root abscess is not necessarily associated with more virulent microorganisms.

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Br Heart J 1992;68:221–2

Dilated cardiomyopathy associated with chronic overuse of an adrenaline inhaler

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Abstract

Endogenous catecholamines in excess are known to cause dilated cardiomyopathy. A patient presented with dilated cardiomyopathy after many years of overusing an adrenaline inhaler.

Pathological features and a considerable improvement in myocardial function after withdrawal implicated the exogenous catecholamine excess in the pathogenesis of the cardiomyopathy.

(*Br Heart J* 1992;68:221–2)

Catecholamine induced cardiomyopathy is a recognised complication of phaeochromocytoma.[1] We report a case in which excessive self medication with an adrenaline containing inhaler used for asthma resulted in a similar clinical condition.

Case report

A 44 year old seaman presented with a short history of increasing breathlessness and wheeze. He had had asthma since childhood, smoked 30 cigarettes a day, and drank less than 20 units of alcohol per week.

On admission he was taking one tablet of Franol (11 mg ephedrine hydrochloride, 8 mg phenobarbitone, 120 mg theophylline) three times daily and a Brovon inhalant spray (0·5% adrenaline, 0·14% atropine methonitrate, 0·88% papaverine hydrochloride) taken as required. Although the maximum recommended dose of the Brovon inhaler is three puffs a day, our patient was in the habit of using the inhaler up to 40 times a day and had done so for 20 years. He had resisted attempts by his general practitioner to convert him to a salbutamol inhaler, which he found lacked effect.

On examination he was obese and tachypnoeic at rest with tachycardia of 120 beats per min. The chest was hyperexpanded with intercostal muscle indrawing and widespread inspiratory and expiratory wheeze. The peak expiratory flow rate was 130 l/min. Arterial blood gases measured while he was breathing air were pH 7·34, Po_2 8·8 kPa, Pco_2 7·0 kPa. A chest *x* ray film showed cardiomegaly (cardiothoracic ratio (CTR) 205/330) with generalised increase in lung markings; an electrocardiogram showed P pulmonale, right axis deviation, and clockwise rotation.

The patient was admitted to hospital. Treatment with the Brovon inhaler and Franol were stopped and he was treated with nebulised salbutamol, ipratropium bromide and oral theophylline. As a result of these measures the peak expiratory flow rate rose to 200 l/min but he remained very breathless. Examination five days after admission showed signs of congestive cardiac failure. The jugular venous pressure was elevated by 8 cm, there was moderate ankle oedema, and a third heart sound. A chest *x* ray now showed considerable pulmonary venous congestion.

The clinical features of congestive cardiac failure improved after treatment with diuretics and captopril. Cross sectional echocardiography showed dilated right and left ventricles with poor systolic function and an isotope ventriculogram showed a left ventricular ejection fraction of 7%. Serum ferritin and thyroid function tests were normal. Concentrations of C3 and C4 were normal, double stranded DNA titre was 0·8 mg/litre, and serological tests for viruses were negative.

Cardiac catheterisation showed a grossly dilated left ventricle with global impairment of systolic function. The ventricular end diastolic pressure was 30 mm Hg and there was moderate pulmonary hypertension with a pulmonary artery pressure of 60/40 (mean 45) mm Hg.

Light microscopy of three right ventricular biopsy specimens obtained by the same procedure showed variation in size of myocardial cells with hypertrophy, nucleomegaly, and focal vacuolation of the fibres. There was no necrosis or inflammatory infiltrate. Electron microscopy studies confirmed the presence of contraction bands and showed focal disruption of myofibrillar architecture with notable lipochrome deposition.

The patient continued to improve with oral diuretics and an angiotensin converting enzyme inhibitor and chest *x* ray film three months later confirmed noticeable improvement in the congestive changes (CTR 180/330) (figure). An isotope ventriculogram six months after use of the Brovon inhaler was stopped showed that the left ventricular ejection fraction had risen to 17%.

Discussion

Myocarditis and myocardial impairment have been reported after exposure to high concentration of endogenous[2 3] and exogenous[4] catecholamines. In laboratory animals the histological picture is similar whatever the catecholamine or the route of administration, and the severity and extent of the damage is

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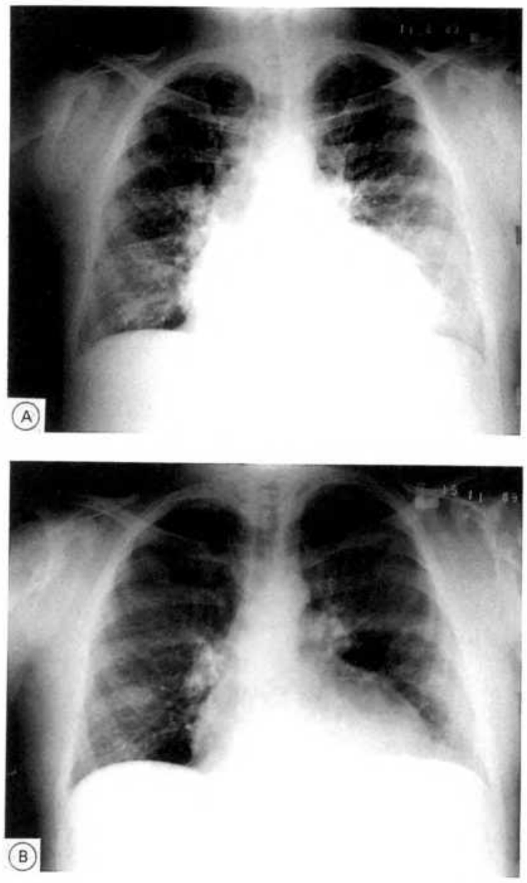

Chest x ray films five days (A) and three months (B) after presentation. Pulmonary congestion improved and the cardiothoracic ratio fell from 205/330 (62%) to 180/330 (54%).

determined by the dose and the duration of exposure.[5]

Myocardial toxicity was implicated in the rise in asthma mortality associated with the use and misuse of aerosols containing sympathomimetic bronchodilators,[6] and transient myocardial ischaemia and myocardial infarction have also been described in asthmatic patients who use isoprenaline inhalers at therapeutic doses.[7]

Catecholamine mediated myocardial toxicity was implicated in sudden death in glue sniffers who misused substances that sensitised the heart to endogenous catecholamines.[8] Dilatated cardiomyopathy associated with solvent abuse has also been reported.[9,10]

The dilated cardiomyopathy associated with phaeochromocytoma is thought to be due to chronic exposure to high concentrations of catecholamines. The pathogenesis is not clear but probably involves ischaemia, due to catecholamine induced vasoconstriction and reduced coronary blood flow,[11] and cell membrane damage caused by the toxic effects of metabolites and cytotoxic free radicals produced by oxidation of catecholamines.[12]

We believe that the chronic overuse of an adrenaline inhaler caused a similar form of cardiomyopathy in our patient. The histological lesions were not specific but they accorded with those found in dilated cardiomyopathy. Postmortem studies of patients dying of phaeochromocytoma showed active myocarditis in some and myocardial fibrosis in others.[2] The limitation of sampling in biopsy procedures precludes exclusion of an inflammatory component; but in studies of myocardial biopsy specimens in dilated cardiomyopathy the frequency of myocarditis seldom exceeded 5%.[13] Moreover, if catecholamine toxicity is mediated through membrane damage an inflammatory component may be an inconstant feature. Lipochrome, seen in electron microscopy, is a common accompaniment to cell ageing, and was notable in our patient. This may relate to increased membrane turnover, accelerated by free radical damage to the membranes.

The reversibility of acute myocardial impairment after a phaeochromocytoma crisis[3] and the lessening of cardiac failure in catecholamine cardiomyopathy after successful surgical removal of phaeochromocytoma have been emphasised,[14,15] so the rise in ejection fraction (from 7 to 17%) would also tend to support our contention. As far as we know this is the first description of a dilated cardiomyopathy caused by exogenous catecholamines.

The prescription of inhalers containing adrenaline has declined dramatically since the concern over their role in asthma deaths in the 1960s and Brovon inhalant solution was withdrawn in October 1989. Inhalant solutions containing adrenaline are, however, still marketed and the dangers of overusing these products must be recognised.

We thank Dr K McLaren for helpful advice regarding the significance of the histological lesions and Dr T M J Griffin for analysing the nuclear ventriculograms and providing the illustrations.

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TECHNOLOGY

Validation of the beat to beat measurement of blood velocity in the human ascending aorta by a new high temporal resolution Doppler ultrasound spectral analyser

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Abstract

***Objective*—To develop and validate a high temporal resolution spectral analysis system for Doppler measurements of blood velocity in the ascending aorta.**

***Design*—An observational laboratory and clinical study comparing Doppler velocity-based measurements with fluid collection, electromagnetic flow catheters and probes, and thermodilution.**

***Setting*—Tertiary referral cardiology unit and cardiac catheter laboratory.**

***Patients*—Patients undergoing routine cardiac catheterisation for ischaemic heart disease, cardiac failure, and primary pulmonary hypertension.**

***Results*—There was good agreement between Doppler-derived and electromagnetic cuff or catheter measurements of velocity in an experimental flow rig (SD of differences 4·75% for velocity integral) and in the patients (SD of differences 4% for velocity integral). There was also reasonably good agreement between simultaneous Doppler-derived and thermodilution-estimated cardiac output measurements in patients undergoing cardiac catheterisation (SD of differences 12·6%).**

***Conclusions*—This new method of high temporal resolution spectral analysis improves the resolution of rapidly changing blood velocities and may improve the ability to describe blood velocity patterns in the ascending aorta.**

(*Br Heart J* 1992;68:223–9)

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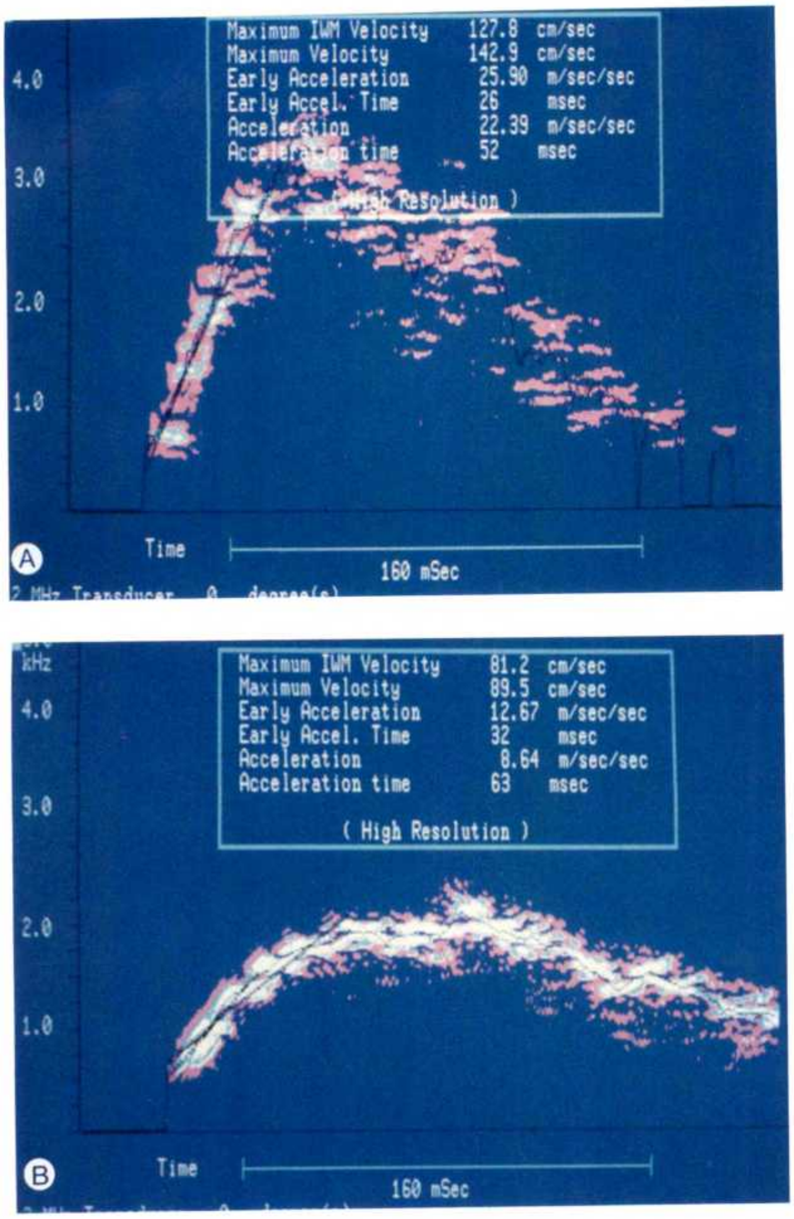
Doppler ultrasound has been used extensively in the assessment of normal and abnormal flow patterns in humans.[1] Although for many routine clinical uses continuous wave Doppler machines are often adequate, to obtain quantitative information on the pattern of blood velocities in the heart or ascending aorta accurate localisation of the sampled velocity is important; hence the distance resolution of pulsed wave Doppler ultrasound is critical. In addition, the use of blood velocity estimates to calculate volume flow, blood acceleration, or the pattern of the aortic velocity wave requires good temporal as well as spatial resolution. Conventional combined Doppler echocardiographic machines either share time between the Doppler and imaging modes, use the same transducer with compromised characteristics for both imaging and Doppler ultrasound, or have low temporal resolution spectral analysers (with sampling every 5–20 ms).

Some of the simpler methods of spectral analysis used in early studies are subject to systematic errors. The zero-crossing detector, for example, can miss high frequency signals when they are superimposed on low frequency signals, because the higher frequency sound wave may not cause the pressure signal to cross zero. The most accurate method of spectral analysis is complete resolution of the different spectral components by fast Fourier transformation (FFT). FFT is now available in real-time computer processing because of the development of powerful minicomputers.

Temporal resolution in spectral analysis can be improved by more frequent FFT analyses, but each time bin must be large enough to include one full cycle of the lowest frequency to be resolved. To detect frequencies down to 100–200 Hz, therefore, the time bin can be reduced to no shorter than 5 ms. Even this resolution may be inadequate to resolve changing blood velocities during the acceleration phase of cardiac ejection because the blood velocity varies from zero to 1–1·5 ms in 50 ms or less. We have developed, therefore, a system with shifting analyses to improve time resolution.[2]

Physiologically it may be important to resolve blood velocities to this greater degree because turbulence and rapidly changing velocities in blood flow can be better detected and quantified. It has been proposed that turbulence may be important in the development of atherosclerotic plaques[3] as well as contributing to the impedance to ejection of blood by the ventricle.[4] Much has been written on the importance of aortic blood acceleration in the assessment of left ventricular function,[5–7] yet little attention is directed to the problems of accurate measurement of aortic blood acceleration. Acceleration is variously defined as the mean acceleration over the time from velocity onset to peak velocity,[8] the mean



Maximum IWM Velocity	127.8	cm/sec
Maximum Velocity	142.9	cm/sec
Early Acceleration	25.90	m/sec/sec
Early Accel. Time	26	msec
Acceleration	22.39	m/sec/sec
Acceleration time	52	msec

(High Resolution)

Maximum IWM Velocity	81.2	cm/sec
Maximum Velocity	89.5	cm/sec
Early Acceleration	12.67	m/sec/sec
Early Accel. Time	32	msec
Acceleration	8.64	m/sec/sec
Acceleration time	63	msec

(High Resolution)

Figure 1 A high resolution Doppler spectral display blood velocity in the ascending aorta in two healthy individuals at rest. (A) a 17 year old woman and (B) a 47 year old man. Single beats were analysed off-line by the high resolution mode. The Y axes are marked in kHz representing the Doppler frequency shifts, which are directly proportional to the velocity of blood in the direction of the ultrasound. Time is marked on the X axis. The table at the top is a summary of the analysis of various variables derived from the single beat shown. IWM, intensity weighted mean.

acceleration over the initial part of the acceleration phase when acceleration seems to be close to constant,[8–10] or the "peak instantaneous acceleration".[6] All three methods are subject to considerable errors because of the low temporal resolution of previous spectral analysers. Figure 1 shows that the upstroke of aortic blood velocity is often curvilinear with no clear point of peak velocity. Acceleration is therefore subject to considerable errors when there is noise at the point of peak velocity. No information can be obtained on the rate of change of velocity before the high pass filter (100–400 Hz), and hence acceleration based on the first half of the acceleration phase may be based on only 20–25 ms of data and may therefore depend on only two or three separate spectral analyses, so that noise in any one time bin would cause considerable uncertainty in the overall assessment of acceleration. Without high temporal resolution spectral analysis measurements of "instantaneous peak acceleration" are even more liable to error and artefact in that instantaneous peak acceleration effectively means the greatest change in velocity between any two time bins and hence is extremely subject to noise in either time bin, especially the first where no velocities below the high pass filter can be detected. It is also fallacious to refer to peak acceleration as being "instantaneous" when temporal resolution is as low as 5–20 ms and changes in aortic blood velocity can occur over less than 5 ms.

Methods

DOPPLER EQUIPMENT

These studies were performed with standalone non-imaging Alfred or Pedof Doppler ultrasound transducers (Vingmed, Norway) with a 2 MHz probe, and a spectral analysis program specifically developed in the hardware environment of a Texas Instruments personal computer (Texas Instruments, Texas, USA). The analyser design and specifications have been described.[2 11] We have improved the temporal resolution of the spectral analyser by storing the original reflected ultrasound signal directly to computer memory, while simultaneously displaying the on-line spectrally analysed signal to aid signal acquisition.[2] At the end of signal acquisition the original ultrasound information is re-analysed in 5 ms bins, followed by repeated re-analysis with the bin being shifted 0·1 ms each time. This allows a full 5 ms of signal to be analysed each time, but also allows rapidly changing frequencies to be resolved because the time bins shift only 0·1 ms at a time. The resulting temporal resolution lies between 0·1 and 5 ms, and is approximately 1 ms.

VALIDATION AGAINST PURE SOUND FREQUENCIES

The spectral analyser received pure sound signals from a high frequency sweep generator model 144 (Wavetek, USA) with static and changing frequencies. We compared the frequency resolution and ability to follow changing frequencies of a commercial analyser (Doptek, Chichester, UK) on fast and slow sweep settings, the Texas instruments analyser with normal on-line spectral analysis resolution, and the Texas instruments analyser with immediate off-line high temporal resolution analysis. We studied the ability to resolve frequencies varying between 0 and 1 kHz by using square wave pulses between 0 and 1 kHz, sweeps between the two frequencies, and continuous triangular waves oscillations between the two frequencies.

VALIDATION AGAINST A FLOW RIG

A flow rig was designed (fig 2) to mimic the ascending aorta of adult man. It used a pulsatile pump to eject a suspension of Sephadex. At a range of pump stroke distances of 38–54 cm and power settings of 6 to 15 V. Five pump beats were measured by three methods: Dop-

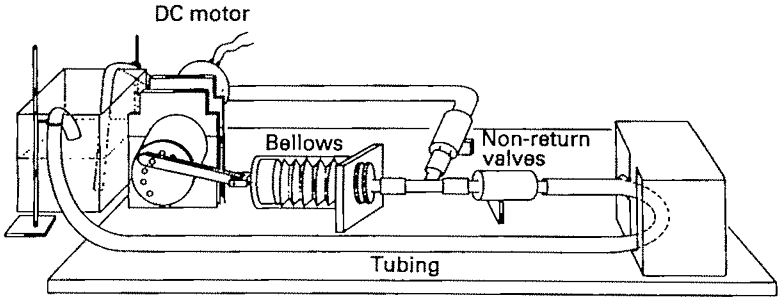


Figure 2 Pulsatile flow rig used to test Doppler velocity and flow measurements against electromagnetic cuff measurements and volume flow collection.

pler ultrasonic measurement of fluid velocity, electromagnetic cuff (Medical Flow Meter System with SEM 275, Feltham, Middlesex) measurement of fluid velocity, and volume flow by fluid collection. The Doppler ultrasound was focused so that the pulse volume recorded velocities occurring as the suspension travelled through the electromagnetic cuff, the internal diameter of which was known. Both Doppler and electromagnetic velocity integrals were converted to volume estimates by multiplication with the internal cross sectional area of the electromagnetic cuff. For the comparison of Doppler and electromagnetic measurements both peak flow and stroke volume were compared, and both measurements of volume flow were compared with absolute flow collected over five beats.

VALIDATION OF VELOCITY VARIABLES IN PATIENTS

In six men with coronary artery disease (aged 52–73) diagnostic cardiac catheterisation was followed by insertion of an electromagnetic flow catheter to the ascending aorta and simultaneous readings were obtained by the electromagnetic catheter (Mills catheter with SEM 275 analyser, Feltham, Middlesex) and pulsed wave Doppler ultrasound of blood velocity in the ascending aorta from the suprasternal approach. Unselected cardiac beats (≥ 100) were recorded for each subject at rest and during various procedures including: programmed electrical stimulation producing extrasystoles and post-extrasystolic accentuated complexes; head up and head down tilting; and inotropic drug stimulation (intravenous milrinone). The interventions with vasoactive drugs were part of routine management or part of separate research protocols for which ethical approval and patient consent had been obtained.

VALIDATION OF VOLUME FLOW CALCULATIONS IN PATIENTS

In 11 patients undergoing right heart catheterisation 64 simultaneous thermodilution (Gould haemodynamic profile computer) and Doppler-derived measurements of cardiac output were obtained at rest and after various procedures such as head up and head down tilting, inotropic drug stimulation (intravenous milrinone), and vasodilator drug administration (intravenous prostacyclin or oral nifedipine). The conditions for which the patients were undergoing cardiac catheterisation were ischaemic heart disease (9), congestive heart failure (5), and primary pulmonary hypertension (2). All patients gave informed consent for these studies, for which ethical committee approval had been given. The age range of patients was from 38 to 73 years and all were in stable sinus rhythm.

The aortic cross sectional area was estimated on a separate occasion within 24 hours of the Doppler recording by means of the leading edge to leading edge convention with cross sectionally directed M mode echocardiographic imaging at the level immediately above the sinuses of Valsalva in mid-systole.[12–14]

STATISTICAL METHODS

Comparisons between methods were examined by the method of Bland and Altman.[15] Systematic differences between methods were tested for by Student's *t* test (two tailed), a p value of $\leq 0{\cdot}05$ was regarded as statistically significant.

Results

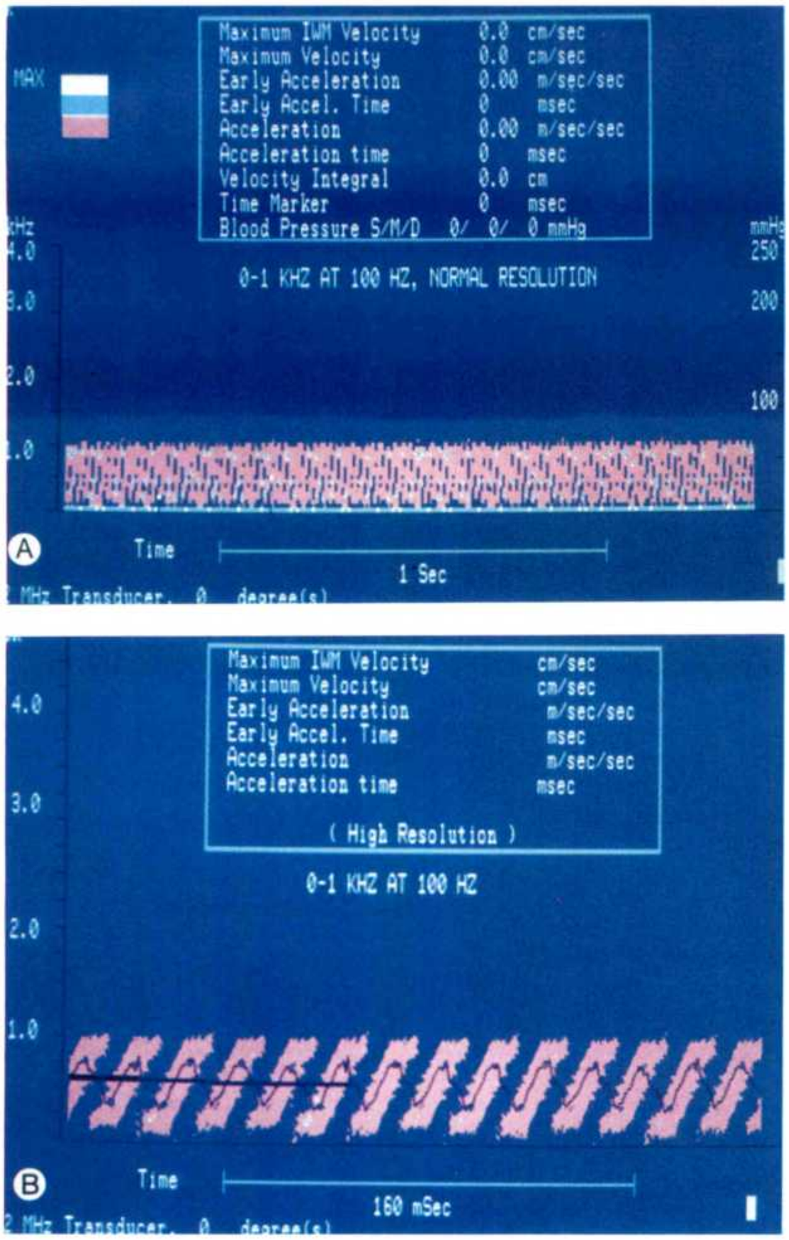
VALIDATION AGAINST PURE SOUND FREQUENCIES

The spectral analyser received pure sound signals with static and changing frequencies. Rapidly changing frequencies were presented to four different modes of spectral analyser: the commercial Doptek analyser on slow and fast sweep settings (spectral analysis time bins of approximately 10 and 5 ms respectively) and the Texas instruments analyser on normal temporal resolution and on immediate off-line high temporal resolution mode. Table 1 shows that as the rate of change of frequency increases the lower resolution modes cease to be able to distinguish the rapidly changing frequencies and the spectral display becomes a blur spreading from 0 to 1 kHz. This is shown in fig 3A in which the signal was analysed by a conventional resolution analyser and is perceived as a wide-band blur of frequencies. The high temporal resolution mode can, however, still determine that the signal is a rapidly changing frequency and the shape of rapidly changing frequency slope is apparent even when it varies from 0 to 1 kHz at a rate of at least 100 times a second (fig 3B). Table 1 lists the changing frequencies that were resolved adequately by each analysis mode.

Table 1 Ability of four modes of spectral analysis temporally to resolve changing frequencies

	Doptek analyser		*Texas analyser*	
Mode	*Slow*	*Fast*	*Normal*	*High Res*
Duration (ms):				
5	—	—	—	1, 2, 3
10	—	1	1	1, 2, 3
15	1	1, 2, 3	1, 2, 3	1, 2, 3
20	1, 2, 3	1, 2, 3	1, 2, 3	1, 2, 3

1 = adequately resolved a square pulse of 1 kHz that lasted the duration specified under the column duration; 2 = adequately resolved a sweep between 0 and 1 kHz that lasted the same duration; and 3 = adequately resolved a triangular wave continually varying between 0 and 1 kHz with each 0 to 1 to 0 kHz cycle lasting the duration specified under the duration column. Where none of the signals was adequately resolved a minus sign is shown.



Maximum IWM Velocity 0.0 cm/sec
Maximum Velocity 0.0 cm/sec
Early Acceleration 0.00 m/sec/sec
Early Accel. Time 0 msec
Acceleration 0.00 m/sec/sec
Acceleration time 0 msec
Velocity Integral 0.0 cm
Time Marker 0 msec
Blood Pressure S/M/D 0/ 0/ 0 mmHg

0-1 KHZ AT 100 HZ, NORMAL RESOLUTION

Maximum IWM Velocity cm/sec
Maximum Velocity cm/sec
Early Acceleration m/sec/sec
Early Accel. Time msec
Acceleration m/sec/sec
Acceleration time msec

(High Resolution)

0-1 KHZ AT 100 HZ

Figure 3 Frequency signals varying from 0 to 1 kHz at 100 times per second (each sweep lasting 10 ms) analysed on the Texas Instruments analysis system with (A) normal resolution and (B) high resolution modes. During the normal resolution mode the signal is blurred whereas in high resolution mode the saw-tooth variation in frequency can be resolved.

Table 2 Results of flow rig experiment

	Electromagnetic cuff		*Doppler*	
Run	*PF (ml/s)*	*SV (ml)*	*PF (ml/s)*	*SV (ml)*
1	90·4	68·8	101·9	70·4
2	141·4	73·2	149·9	77·3
3	186·0	80·7	187·6	81·8
4	239·6	81·5	223·6	81·3
5	80·8	55·6	86·0	56·1
6	115·6	61·0	121·6	60·4
7	145·6	64·6	148·1	67·0
8	190·8	69·2	185·7	69·5
9	104·8	81·9	114·0	76·5
10	164·2	89·2	163·1	84·3
11	222·2	91·5	211·3	91·0
12	277·0	95·8	258·4	91·0
13	205·2	75·6	191·4	66·6
14	123·6	37·3	111·2	36·6

Each value is the mean of five beats per run. Runs 1–4 were performed with the stroke distance of the piston set at 46 cm and the power of the pump progressively increased from 6·0 V to 9·0, 12·0, and 15·0 V. Runs 5–8 used the same progressive voltage settings with stroke distance at 38 cm, and for runs 9–12 the stroke distance was set at 54 cm. Run 11 was at 12·0 V at a stroke distance 54 cm with constriction of the outflow tubing and run 12 was similar with constriction of the inflow tubing. PF, peak flow; SV, stroke volume.

VALIDATION AGAINST A FLOW RIG

Table 2 compares measurements of stroke volume and peak flow by the electromagnetic cuff and the Texas Instruments Doppler system in the flow rig. The methods were compared according to the recommendations of Bland and Altman.[15]

They did not give significantly different results (electromagnetic first): mean (SD) peak velocity 163·4 (59·1) ml/s compared with 161·0 (51·0) ml/s (NS); mean (SD) stroke volume 73·3 (15·6) compared with 72·1 (14·7) NS.

Table 3 shows the comparison between either method and the five beat pump volume. Table 4 shows the comparison by Bland and Altman's method. Other conditions mimicking clinical conditions were investigated including outflow (run 13) and inflow constriction (run 14) (table 3). The shapes of the velocity profiles shown by Doppler and electromagnetic cuff were similar (see single pump beat in fig 4).

VALIDATION OF VELOCITY VARIABLES IN VIVO

Figure 5 shows the comparisons between electromagnetic catheter derived and Doppler derived peak velocity, acceleration, and stroke distance for 621 unselected beats from all subjects (521 beats for acceleration because in one subject electrical interference on the tape made the Doppler estimate of acceleration impossible) using the Bland and Altman plot method. The mean and standard deviations of the differences between the Doppler and electromagnetic catheter methods were −0·05 (6·5)% for peak velocity; −0·4 (8·7)% for stroke distance; and −1·9 (13·7)% for acceleration. Estimates of minute distance were the averages of 10 consecutive cardiac beats. The mean ± (SD) of differences between the two methods was −0·67 (3·6)% (fig 6).

Table 5 shows the correlation coefficients between variables measured by Doppler and electromagnetic methods for individual subjects.

VALIDATION OF VOLUME FLOW CALCULATIONS IN VIVO

The results of all simultaneous measurements between Doppler derived cardiac output and

Table 3 Volume flow estimates in the rig by electromagnetic cuff, Doppler, and fluid collection

Run	*E/M cuff (l/min)*	*Doppler (l/min)*	*Fluid collection (l/min)*
1	1·21	1·24	1·15
2	2·04	2·15	1·97
3	3·07	3·11	2·92
4	3·95	3·94	3·77
5	1·00	1·00	0·89
6	1·70	1·68	1·53
7	2·46	2·55	2·32
8	3·35	3·36	3·23
9	1·41	1·32	1·21
10	2·48	2·34	2·30
11	3·48	3·46	3·25
12	4·56	4·33	4·34
13	2·89	2·53	2·70
14	1·44	1·41	1·35

See footnote to table 2 for explanation of runs.

Table 4 Volume flow and flow variables expressed as the mean absolute and percentage differences between methods and the standard deviations of these differences according to the recommendations of Bland and Altman (1986)[15]

	Mean difference	*SD difference*
	Flow rate (l/min)	
D – EM:		
Absolute	−0·041	0·124
Percentage	−1·43	4·75
D – Coll:		
Absolute	0·106	0·101
Percentage	5·38	4·69
EM – Coll:		
Absolute	0·147	0·054
Percentage	6·81	3·24
	Peak flow (ml/s)	
D – EM:		
Absolute	−2·39	10·29
Percentage	−1·60	6·79
	Stroke volume (ml)	
D – EM:		
Absolute	−1·16	3·98
Percentage	−1·44	5·37

Coll, collected flow; D, Doppler; EM, electromagnetic cuff.

that obtained by thermodilution were plotted according to the Bland and Altman method (fig 7). The mean and standard deviation of differences between methods (thermodilution − Doppler) was 0·35 (0·67) l/min. There was a small but significant underestimation by the Doppler method compared with the thermodilution method (5·1 (1·4) l/min compared with 5·5 (1·2) l/min, $p < 0.01$).

Discussion

These findings show the accuracy of pulsed wave Doppler estimates of the most commonly used velocity variables (peak velocity, stroke distance, and acceleration) against electromagnetic cuff and catheter measurements in both an artificial flow rig and in the human aorta. The Doppler method we used with a new high resolution spectral analysis system gave an accurate independent measure of blood velocity. The accuracy was maintained for peak velocity and the velocity integral (stroke distance), but there was much more variation between methods for acceleration.

The Doppler method gave accurate estimates of volume flow in an artificial flow rig compared with the absolute flow measurement when the cross sectional area of the flow rig tubing was known. In humans volume flow was compared with thermodilution estimates (through a pulmonary artery catheter), which themselves are subject to a fair degree of variability and are sources of inaccuracy.[16] Despite this proviso the volume flow estimates obtained by the Doppler method compared reasonably well with the thermodilution method in the subjects we studied, and these results accord with reports of similar comparisons of thermodilution and continuous

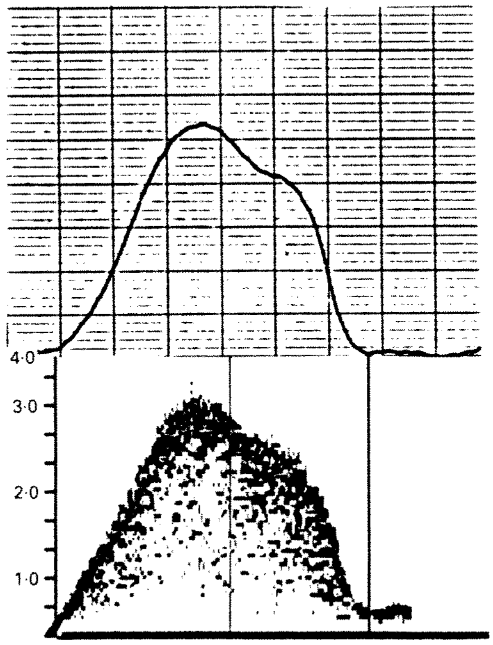


Figure 4 Flow profile from the flow rig experiment showing the same beat measured by electromagnetic cuff (top) and by Doppler (bottom). The electromagnetic signal is displayed as a single line (average flow) output whereas the Doppler measurement is the spectral display of the Doppler frequency shift (proportional to velocity). The figure shows the similarity in the shape of the same beat estimated by the two techniques. Comparability of actual measurements is described in the text.

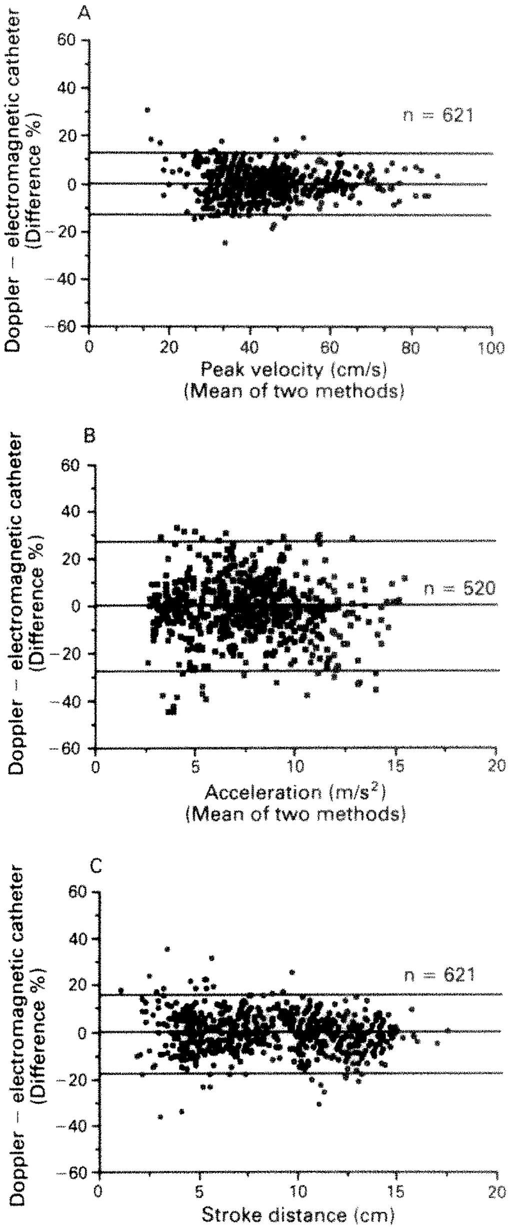


Figure 5 Comparison of (A) peak velocity, (B) acceleration, and (C) stroke distance between Doppler estimate and electromagnetic catheter measurement for all beats analysed in six subjects. Results are plotted as Bland-Altman plots. The middle line is the mean difference between methods and the two outer lines are the 95% confidence intervals for the differences between methods.

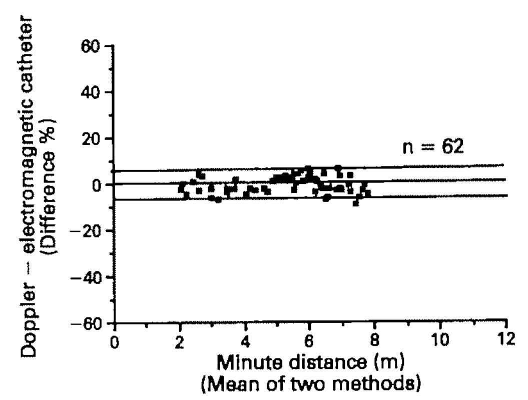


Figure 6 Comparison between minute distance for all 10 beat averages recorded by Doppler and by electromagnetic catheter in six subjects. See legend to fig 5 for explanation.

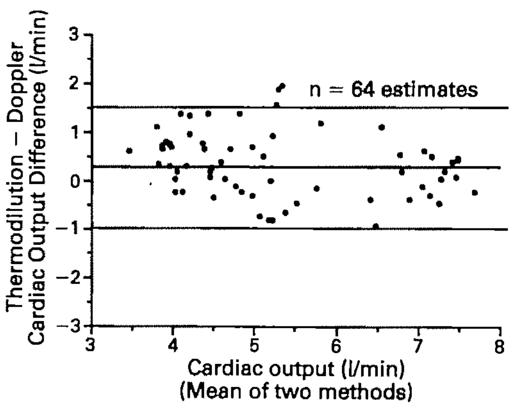


Figure 7 Bland-Altman plot for all paired measurements of cardiac output from Doppler derived measurements and simultaneous thermodilution estimates. The middle line is the mean difference between methods and the two outer lines are the 95% confidence intervals of the differences between methods.

wave[17–19] and pulsed wave Doppler.[13 20 21] These and more recent reports[10 22 23] give standard deviations of differences compared with simultaneous thermodilution estimates of cardiac output in the range 8–22%.

Inaccuracies in estimating volume blood flow owe more to inaccuracies in the measurement of aortic cross sectional area than to the evaluation of blood velocity itself. This was shown by a greater similarity in our results between electromagnetic and Doppler velocity variables in man and the flow rig than was seen between either of the velocity based methods and thermodilution. The small (<10%, but significant) underestimation by Doppler compared with thermodilution in both stroke volume and cardiac output is probably caused by errors in measurement of the cross sectional area of the ascending aorta.

There is no ideal reference standard for human volume blood flow measurements, but it seems that the Doppler method is a good technique in subjects without turbulent blood flow in the ascending aorta. If we assume that the cross sectional area of the ascending aorta does not change appreciably in the short to medium term or with drugs or moderate blood pressure changes[24] then the ability of the Doppler method to quantify proportional changes in cardiac output will be even greater than its ability to give a single measure of cardiac output.

The advantages of high resolution spectral analysis can be seen by the greater temporal resolution shown when a pure frequency signal was rapidly changed. Spectral analysers with larger time bins, and hence lower temporal resolution, artificially blur rapidly changing blood velocities, and hence no description of an instantaneous maximal acceleration is obtainable. Our results support the approach of averaging a period of the acceleration phase over which an adequate number of data points can be accumulated to give a reliable estimate of acceleration. The new analyser we describe, when used in off-line high resolution mode increases the temporal resolution of Doppler signals substantially. This allows more detailed description of rapidly changing blood velocities, which would be useful in assessing acceleration, turbulence, and spatially dispersed blood velocity profiles. Most Doppler recordings in cardiological examinations are obtained on machines that combine echo and Doppler and in which the spectral analysers more commonly use a 10 ms time bin for FFT analysis (similar to the slow sweep setting of the Doptek analyser described here) rather than the smaller 5 ms time bins used in the Doptek fast sweep mode or the on-line normal resolution in our new analyser and the < 1ms time bin of the high resolution mode off-line analyses. The results in table 1 show how low is the temporal resolution of these conventional analysers.

We found that acceleration was much less reliable and showed more between method variation than either stroke distance or peak velocity, and we argue that it is the least reliable of the Doppler-derived velocity measurements.

There is a need for accurate blood velocity measurements in the ascending aorta and other parts of the circulation, both to provide a relatively reliable, safe, and repeatable measure of volume flow rate, and also to investigate non-invasively blood velocity patterns themselves. Accurate non-invasive measurements of blood velocity by Doppler may be the best way of obtaining information on aortic flow patterns, blood flow turbulence, and the influence of pressure-reflected waves on ventriculoaortic coupling in heart failure and other conditions.

Table 5 Correlation coefficients between electromagnetic catheter and Doppler estimates for individual subjects.

Subject	*Peak velocity*	*Acceleration*	*Stroke distance*
1	0·96	0·84	0·97
2	0·92	0·83	0·94
3	0·98	NA	0·95
4	0·90	0·84	0·80
5	0·86	0·80	0·94
6	0·94	0·90	0·90

NA, not available because of electrical interference on tape recording.

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Br Heart J 1992;68:230–5

TECHNOLOGY

A new system for ambulatory pulmonary artery pressure recording

J Simon R Gibbs, Donald MacLachlan, Kim M Fox

Abstract

***Objective*—To develop a complete system for the measurement, recording, and analysis of ambulatory pulmonary artery pressure.**

***Design*—The new system consists of a pulmonary artery catheter, an ambulatory recorder, and a desktop computer. Pulmonary artery pressure is measured by a micromanometer tipped catheter with an in vivo calibration system to allow correction for zero drift. This catheter is plugged into a small battery powered recorder. The recorder has two input channels, one for pressure and one for an event marker. The pressure wave is sampled 32 times/s, processed by an in built computer, compressed, and stored in semiconductor memory. On completion of a recording, data is transferred from the ambulatory recorder through a serial data link to an Acorn Archimedes desktop computer on which further data processing, statistical analysis, graphics, and printouts can be obtained.**

***Results*—The system has been used in 18 patients, with technically successful recording in 14, less than 15 minutes of data loss in three, and 12 hours of data loss in one.**

***Conclusions*—A new system for ambulatory pulmonary artery monitoring has been developed and used clinically with success. It may provide new perspectives on the pathophysiology of disease as it applies to everyday life.**

(*Br Heart J* 1992;68:230–5)

The pulmonary circulation is somewhat inaccessible for haemodynamic measurements, but this should not belittle its importance in the pathophysiology of cardiovascular and pulmonary disease. As pulmonary artery pressure undergoes large changes with alterations in posture and activity, ambulatory recordings provide more information than single measurements made in a catheter laboratory.

Ambulatory pulmonary artery pressure has been used to investigate pathophysiological aspects of heart failure,[1-3] coronary artery disease,[4-6] and pulmonary hypertension.[7] It may be used to study the effects of medical and surgical treatments. Because pulmonary artery diastolic pressure is a good estimate of left ventricular end diastolic pressure in the absence of mitral valve disease or raised pulmonary vascular resistance,[8 9] this technique may be used to assess left ventricular function in ambulant patients.[10 11] Ambulatory monitoring of the pulmonary artery has been used in a few cases both in our own studies and by others to guide clinical decisions.[12]

The application of ambulatory monitoring of pulmonary artery pressure has been limited because of the lack of a suitable catheter for long-term pressure recording and a data recording and analysis system specialised for pulmonary artery pressure. To make this technique practical we have developed a complete system for measurement and recording of ambulatory pulmonary artery pressure.

Patients and methods

DESCRIPTION OF NEW SYSTEM

The new system consists of a pulmonary artery catheter, an ambulatory recorder, and a desktop computer.

Catheter

Pulmonary artery pressure is measured by a 7F NIH catheter (Type 7F/B, Gaeltec Ltd, UK) designed for making continuous long term recordings. The catheter is intended for multiple use and is sterilised either in activated glutaradlehyde (Cidex, Surgikos Ltd, UK) for at least 10 hours, or ethylene oxide.

A pressure transducer is located at the tip of the catheter thus making the tip its own zero reference point and overcoming the difficulty of levelling an external transducer with the catheter tip. As zero drift is an unpredictable property of micromanometer tipped catheters during prolonged recordings, the special feature of this catheter is that it is fitted with an in vivo calibration system to allow correction for zero drift.[13] The calibration is simple to perform: it takes 10 to 15 s and can be performed by medical or nursing staff.

During normal recording the back of the pressure transducer is in contiguity with atmospheric pressure through a luer fitting on the end of the catheter outside the patient (fig 1).

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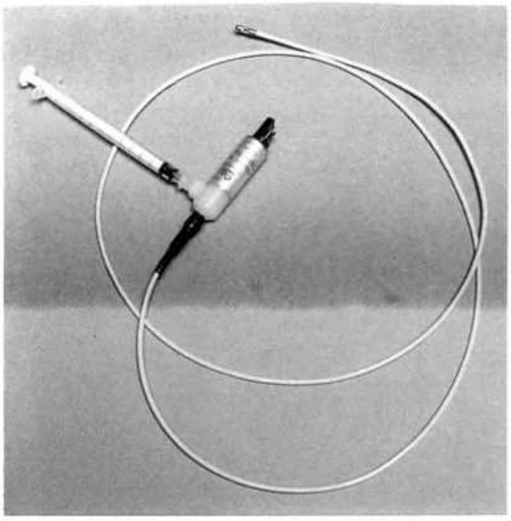

Figure 1 Pulmonary artery catheter showing a 1 ml syringe attached to the external luer fitting as required for calibration. The stainless steel tip houses the transducer.

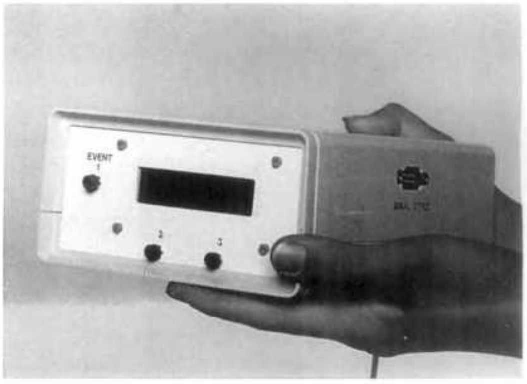

Figure 3 The new ambulatory recorder. Note the three function buttons and the liquid crystal display on the front of the box, and the socket for the serial link to the desktop computer on the side.

The catheter is calibrated during recording by injecting 0·4 ml air from a 1 ml syringe into the luer fitting. This causes a pressure of about 124 mm Hg to be applied not only to the back of the pressure transducer, but also to a second lumen which connects with the opposite side of the transducer and causes the elastomer covering the transducer at the tip of the catheter to be lifted off its surface. The high and equal pressure that now exists either side of the transducer restores it to its zero state. During calibration, pulmonary artery pressure is transiently interrupted by a calibration line (fig 2). When the syringe is removed from the luer lock, pulmonary artery pressure recording restarts automatically.

Because zero drift tends to be largest during the early part of the recording,[13] we calibrate the catheter every 10 minutes for the first two hours, every 20 minutes for the next six hours, and one to two hourly thereafter.

Ambulatory Recorder

The catheter is plugged into a battery powered ambulatory recorder (Type 7MPR, Gaeltec Ltd, UK) which is carried by the patient on a shoulder strap. The dimensions are 188 × 137 × 67 mm and it weighs 850 g including its four size AA batteries that provide sufficient power for 24 hours of recording.

The recorder (fig 3) has three buttons that are used for setting it up at the beginning of recording and one of which is used as an event button during recording. A liquid crystal screen displays the clock time and the amount of memory used. A socket on the side of the box is used to connect it to the desktop computer through a serial link and the catheter connection socket is at the rear of the box.

Figure 4 shows a schematic diagram of the ambulatory recorder. Pulmonary artery pressure can be recorded in the range −30 mm Hg to 223 mm Hg. The analogue pressure signal from the catheter is received by the analogue input board, amplified, filtered to limit the highest frequency to 16 Hz to prevent aliasing, and sampled 32 times/s. This data is processed to reduce the amount of data that has to be stored and then held in a semiconductor memory. This data reduction is important to enable long recordings to be made. Sufficient memory is provided for roughly 12 hours of recording. The memory used for storage of data has a back up power source separate from the main batteries, so that these can be changed without loss of data.

The desktop computer can be connected to the ambulatory recorder through the serial link, which for patient safety is optically isolated. This link is used for three purposes. Firstly, it is used to download recorded data for analysis and storage on magnetic disk. Secondly, it allows the desktop computer to be used to interrogate the recorder and alter its recording parameters before and during recording. Thirdly, it allows the desktop computer to display pulmonary artery pressure in real time. This real time display, which does not undergo any data compression, can be saved on disk and compared later with the compressed data stored in the recorder.

We used an Archimedes desktop computer (Acorn Computers, UK) which is multitasking and particularly suited to this type of application. A minimum of two megabytes of random access memory and a 20 megabyte hard disk are required.

The reference pressure port includes an industrial standard pressure transducer and is used for calibration purposes.

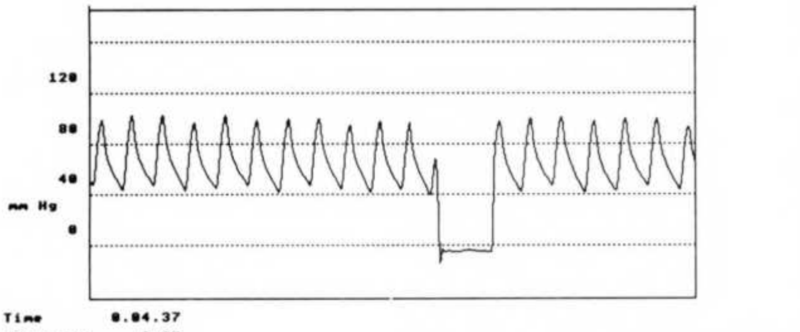

Figure 2 Pulmonary artery pressure recording showing transient interruption by a reference calibration.

Calibration of Ambulatory Recorder

The ambulatory recorder is calibrated with the catheter immediately before catheterisation. The catheter is connected to the recorder and

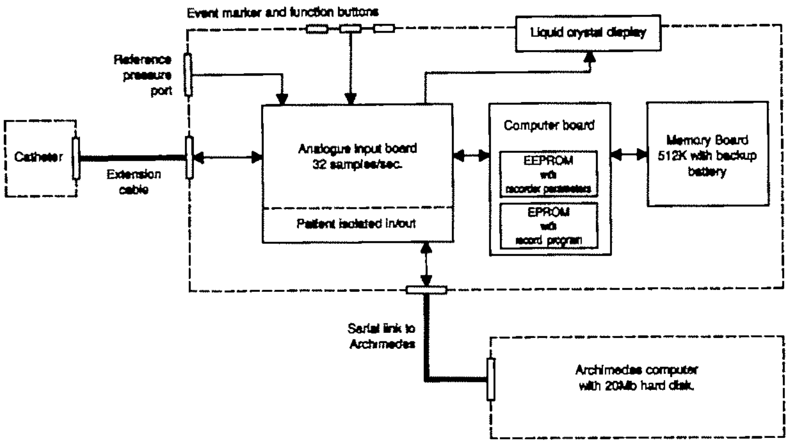
Event marker and function buttons
Liquid crystal display
Reference pressure port
Catheter
Extension cable
Analogue input board 32 samples/sec.
Patient isolated in/out
Computer board
EEPROM with recorder parameters
EPROM with record program
Memory Board 512K with backup battery
Serial link to Archimedes
Archimedes computer with 20Mb hard disk.

Figure 4 Schematic diagram of the ambulatory recording system. EPROM, electronically programmable read only memory; EEPROM, electronically erasable and programmable read only memory.

set to zero, the catheter output being stored in memory. Negative pressure is then applied simultaneously to the catheter transducer through the external luer fitting and to the recorder's own reference standard. When the reference transducer measures a pressure of −100 mm Hg, the catheter output is stored. The system is then ready to use.

Compression of Pressure Data

Data compression presents a particular problem because of the irregular nature of pulmonary artery pressure waves during large amounts of respiratory variation. One consequence of this is that the diastolic pressure of one wave may exceed the systolic pressure of the next.

Figure 5 shows pressure waves composed of equally spaced samples marked by crosses. The number of samples stored may be reduced by using only those marked by circles. If the circles are linked by straight lines, the maximum deviation of the other points from the lines is very small. The algorithm that we have used identifies such data points. The important features of this algorithm are that all recorded points lie on the original curve, and that it tends to select points of inflection so that errors in the subsequent calculation of systolic and diastolic pressure are less than 1 mm Hg. The amount of data stored is further reduced by dynamically varying the number of points recorded with the amplitude of the pressure wave. Over 24 hours this algorithm will typically store between 800 000 and 1 million data points.

As the amount of irregularity of the pulmonary artery pressure waveforms varies between patients, we have validated this algorithm for individual patients by comparing real time recordings made from non-compressed data over the serial link, with the same record compressed within the recorder and replayed later.

Data Analysis and Presentation

With a menu driven programme on the desktop computer, pressure recordings can be analysed, printed, and stored on hard or floppy disks. Firstly, pressure recordings are corrected for zero drift. This requires the operator to validate recorded data visually and identify catheter calibrations. The computer will then automatically recalculate the whole recording by linear interpolation between calibrations. Secondly, heart rate is automatically derived by measuring the distance between pressure wave peaks. Thirdly, event markers, which appear as short vertical lines on the screen display of the pulmonary artery pressure, can be annotated with comments concerning posture and activity from a diary kept during the recording period.

Presentation graphics allow the display of any period of recording from 15 seconds to 48 hours with a summary of the average systolic, diastolic, and mean pulmonary artery pressure as well as heart rate during the specified period. The value of individual data points can be obtained with the aid of a screen cursor.

Patient Studies

We have performed ambulatory recordings with the new pulmonary artery catheter in 36 patients of whom the ambulatory recorder and analysis system described here was used in 18. The age range was 16–68 years and recordings have been made from 10 to 48 hours in duration. Twenty four patients with chronic heart failure, 10 with pulmonary hypertension, and one with breathlessness of unknown aetiology were investigated.

Patients were not given premedication. The catheter was inserted into a subclavian or internal jugular vein through an 8F sheath under local anaesthesia, and positioned in the proximal right or left pulmonary artery under fluoroscopy. The sheath was then withdrawn from the vein and the catheter sutured to the skin and covered with a sterile dressing. All catheterisations were performed by one of us (JSRG). All patients went about unrestricted activities within the confines of the hospital and underwent symptom limited exercise testing during the period of recording.

An ambulatory electrocardiogram was performed simultaneously with two bipolar leads, an anterior lead CM5, and an inferior lead. Recordings on to magnetic tape were made by a

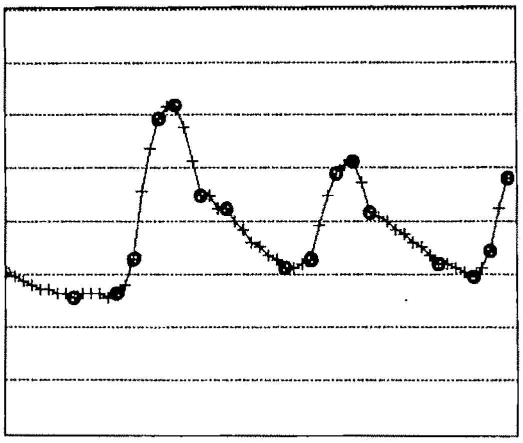

Figure 5 Schematic representation of the data compression algorithm. See text for explanation.

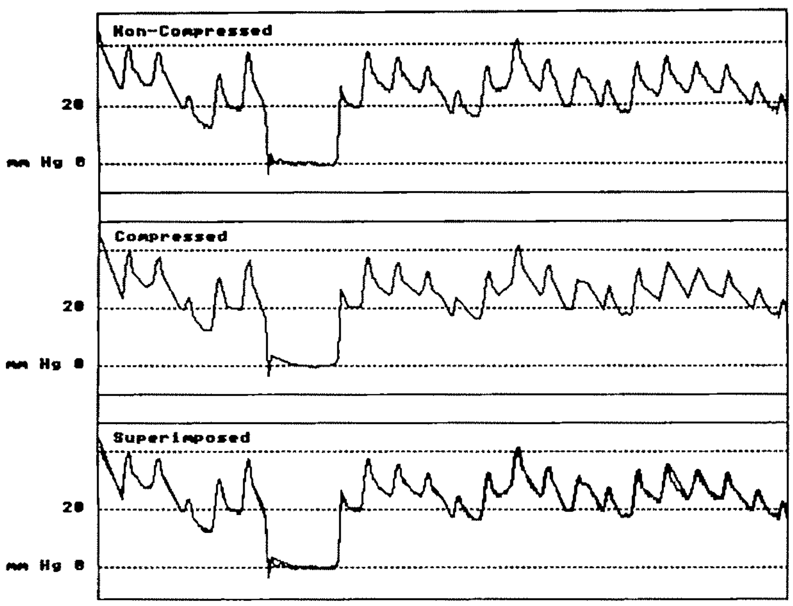

Figure 6 Comparison of compressed (top panel) and non-compressed (middle panel) pulmonary artery pressure recording showing good agreement between systolic and diastolic values when the traces are superimposed (bottom panel).

frequency modulated dual channel recorder (Oxford Medilog II) to detect arrhythmias.

The results of these studies were scrutinised for complications related to catheterisation and technical problems related to the catheter and recording system. Recordings were considered technically satisfactory if no data loss was caused by the catheter or ambulatory recorder during the intended recording period (minimum 24 h). The results of the studies on patients with heart failure have been published elsewhere.[2 3]

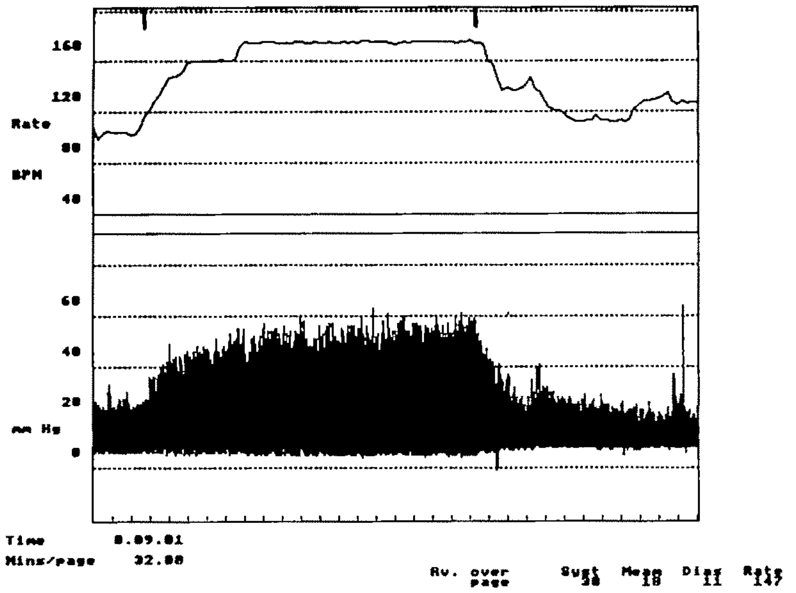

Figure 7 An example of display of a region of interest. The horizontal axis represents 32 min. Heart rate is displayed in the top panel and pulmonary artery pressure in the lower panel. Pulmonary artery pressure is shaded: the upper border is systolic pressure and the lower border is diastolic pressure. Event markers indicating the beginning and end of exercise appear as short vertical lines at the top of the figure. Pulmonary artery pressure rises with exercise and falls rapidly after the end of exercise.

Results

VALIDATION OF DATA COMPRESSION ALGORITHM

Figure 6 shows the result of comparing a recording of non-compressed data with compressed data. This typical excerpt from a recording includes a catheter calibration. Despite data compression the pulmonary artery waveform, shown in the middle panel, is still clearly recognisable. When the non-compressed trace (top panel) is superimposed (bottom panel) on the compressed trace there is a good match and the maximum error between the two traces is <1 mm Hg. This good match was confirmed in multiple comparisons in different patients.

PATIENT STUDIES

No complications were encountered because of catheterisation. In particular, no pneumothoraces, inadvertent arterial punctures, or local or systemic sepsis occurred. There was no clinical evidence of pulmonary embolism or infarction. Some patients had a mild ache at the site of catheter insertion, but this was always relieved by paracetamol and did not restrict their activities. One patient had the catheter removed after 10 hours because of discomfort. Continuous recording of the electrocardiogram showed no sustained disturbance of rhythm during recording of pulmonary artery pressure.

Seven catheters were used in the 36 patients. The maximum recording time for a single catheter was 240 hours. Catheters were discarded if there way any evidence of damage to the shaft or the tip.

Of the 18 patients assessed with the complete system, recordings were technically satisfactory in 14. Data loss occurred because of disconnection of the catheter from the lead connecting it to the recorder in two patients causing data loss of <5 minutes; inadvertent calibration of the recorder after downloading data after 12 hours of recording in one patient resulted in subsequent data loss; and loss of battery power in one patient caused the loss of 15 minutes of data. None of these causes of data loss can be blamed on the recording system itself. As catheter tip impaction in a pulmonary arteriole causes distortion or loss of the pulmonary artery pressure wave, it can be concluded that no such impaction occurred. During exercise tests the pulmonary artery pressure waveform remained undistorted.

Figure 7 shows how a particular region of interest, in this example a treadmill exercise test performed by our patient with unexplained breathlessness, can be displayed. The rise in pressure occurred at the beginning of exercise and there is a rapid fall when exercise stops. Figure 8 shows a 48 hour recording in a patient with chronic heart failure. This patient was investigated as part of a single blind study in which he received placebo during the first half of the recording and xamoterol during the second half. The time the patient was in bed at night is indicated by the horizontal lines. Note how the nocturnal pressure rise on placebo was abolished while the patient was taking xamoterol.

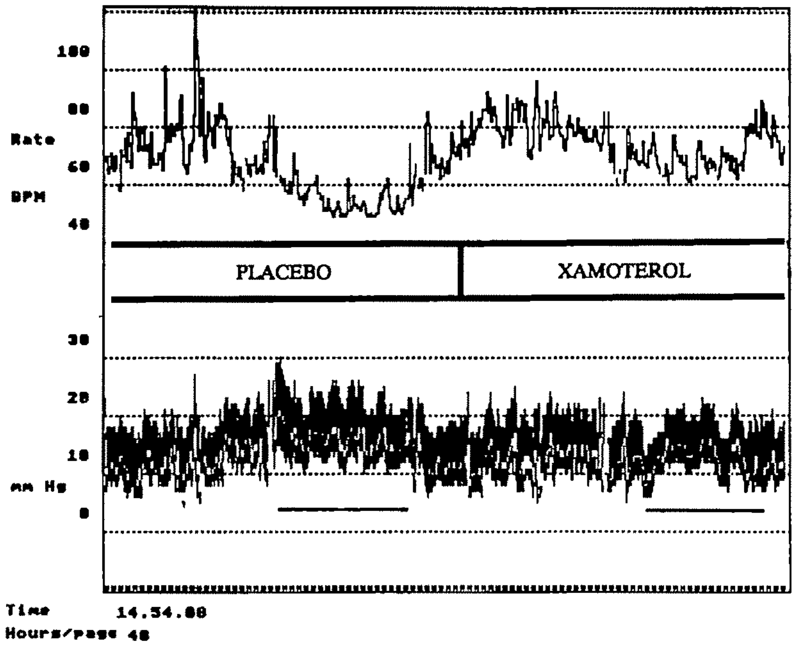

Figure 8 A 48 hour recording of ambulatory pulmonary artery pressure in a patient with chronic heart failure. Heart rate is displayed in the top panel and pulmonary artery pressure in the lower panel. Pulmonary artery pressure is shaded: the upper border is systolic pressure, the lower border is diastolic pressure, and the measured mean is shown as a white line in between. The patient was given placebo during the first 24 hours and xamoterol during the second 24 hours. The horizontal lines indicate the time spent by the patient in bed at night.

Discussion

PULMONARY ARTERY PRESSURE MEASUREMENT

Reliable assessment of pulmonary artery pressure requires catheterisation. It was the partnership of Cournand and Richards and their coworkers who, experimenting first on animals and then on humans, perfected right heart catheterisation and used it to sample blood and measure cardiac output.[14-16] The first recorded pressure tracings in the pulmonary artery of humans were taken in 1944 and thus opened a new era for the study of the pulmonary circulation in health and disease.[17]

Catheterisation of the pulmonary artery and the measurement of the oxygen saturation in blood taken from the pulmonary capillary "wedge" position was achieved by Dexter *et al* and Hellems *et al* while they were investigating congenital heart disease.[18-20] The close relation between the pressure measured in the "wedge" position, the pulmonary venous and left atrial pressure, and the pulmonary artery diastolic pressure was also reported.[11 12 21] It was only a short time before catheterisation was used to investigate physiological problems and to guide medical treatment.[22-24] The value of measuring pulmonary artery pressure in acutely ill patients was recognised,[25 26] and a simple method for catheterising the pulmonary arteries without the need for fluoroscopy was described in 1970.[27] Fluid filled balloon flotation catheters have since remained the standard method for measurement of pressure in the pulmonary artery for research on haemodynamics. Whereas these catheters provide the simplest method of bedside monitoring, the difficulty of levelling an external pressure transducer with the catheter tip during totally unrestricted activities is impractical

AMBULATORY PULMONARY ARTERY PRESSURE MEASUREMENT

Different methods of ambulatory pulmonary artery monitoring have been reported by four other groups. Three of these have used micromanometer tipped catheters,[1 28 29] but only one has attempted to measure zero drift, and published data on their technique is limited.[29] The two methods that have not measured zero drift, including one published by our own laboratory,[28] have not been pursued further.

The fourth group have reported a method in which pressure was measured for 10 to 25 hours with a 5F Goodale Lubin catheter with one end hole and two side holes.[30] The external pressure transducer was calibrated once near the beginning and once near the end of each study. The catheter was linked to a portable transducer-perfusion unit. The investigators experienced difficulties with the catheter clotting despite administration of heparin at a rate of 20 000 IU a day. Twenty per cent of the recordings were affected by artefacts that presumably originated from the fluid filled catheter.

Various recording systems have been employed. The originators of the technique used a digital recorder that averaged systolic and diastolic pressure over consecutive 30 second intervals.[1] The system was unable to record pressure waves and neither visual validation of the recorded data nor beat to beat changes in pressure could be measured. Two groups favoured a miniature tape recorder. One used their own custom written computer programme to digitise and analyse the data,[30 31] and the other an optical writer to playback the data for visual analysis.[28] Our own experience of visual analysis is that it is immensely time consuming.

All of these systems were developed by research workers for their own use. Without a commercially available system ambulatory pulmonary artery pressure recording has been unable to find general application.

The principal application of long-term continuous monitoring of ambulatory pulmonary artery pressure is as a research tool to investigate the natural history and pathophysiology of cardiovascular and pulmonary disease. It may be used to investigate diurnal variation, and the effects of daily activities and specific interventions, such as exercise tests, cold pressor tests, and drug administration, on pulmonary artery pressure. We have recently used ambulatory recordings for spectral analysis.[32]

THE NEW SYSTEM

The purpose of developing a new system for monitoring ambulatory pulmonary artery pressure was to make this technique generally available while overcoming the technical difficulties that have dogged previous investigators. Pressure measurement is accurate and data analysis rapid. Patients do not require anticoagulation.

The limitations of the technique are those of all invasive investigations, but in particular operators should have previous experience of right heart catheterisation and not simply the insertion of flotation catheters. Care should be taken not to advance the catheter too far into the pulmonary artery to a position from which it could migrate and become wedged. Like most invasive investigations the patients require careful monitoring as catheter calibrations should be performed frequently. With the need for more calibrations early in the recording we perform our catheterisations in the morning. Despite the frequent need for calibrations during recording, the brevity of this procedure hardly interferes with the daily activities of patients. During recording a doctor need only be in attendance during specific manoeuvres such as exercise tests. Although our patients were limited to the confines of the hospital, we do not believe that this is strictly necessary. For the forseeable future we shall continue to investigate patients on an inpatient basis. The ambulatory recorder has enough memory for about 12 hours of recording. Although it might be more convenient to store 24 hours of data, 24 hour recordings will not fit on to a single floppy disc for data storage, and it is assumed that investigators will want to archive their data.

In conclusion, a new system for measurement of ambulatory pulmonary artery pressure, recording and analysis has been developed with a micromanometer tipped catheter, an ambulatory digital recorder, and a desk top computer. A data compression algorithm designed to contend with large fluctuations in pulmonary artery pressure has been validated. Measurement of ambulatory pulmonary artery pressure is safe and well tolerated. It may provide new perspectives on the pathophysiology of disease as it applies to everyday life.

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MEASUREMENT

Calculation of aortic regurgitation orifice area by Doppler echocardiography: an application of the continuity equation

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Abstract

The evaluation of aortic regurgitation by current echocardiographic techniques has been qualitative and load-dependent. The area of the regurgitant orifice, which is theoretically independent of haemodynamic conditions, has not been determined non-invasively. In 20 patients with various degrees of aortic regurgitation, this area was determined by use of the continuity equation applied during diastole. The velocity-time integrals were determined at the supravalvar (VTI_s) and regurgitant orifice (VTI_r) levels by pulsed and continuous wave Doppler respectively. The cross sectional area at the supravalvar level (A_s) was also measured by cross sectional echocardiography. The regurgitant orifice is given by: $(A_s \times VTI_s)/VTI_r$. Other non-invasive measurements of the aortic regurgitation severity were also recorded: (*a*) an overall echo score (1–5+) given blindly by two echocardiographers, (*b*) the maximal proximal jet width by colour Doppler, (*c*) left ventricular end systolic and end diastolic volumes and left ventricular mass. The regurgitant area ranged from 0·25 to 1·7 cm^2 and this area accorded with the overall echo score and the maximal proximal jet width measured by colour Doppler.

The aortic regurgitation orifice area can be calculated non-invasively and it may be a quantitative measure of the severity of aortic regurgitation.

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Doppler echocardiography is both sensitive and specific for the detection of aortic regurgitation,[1 2] but quantification of the severity of aortic regurgitation has proved difficult. Earlier studies showed correlation between the severity of aortic regurgitation and various non-invasive assessments by pulsed wave Doppler flow mapping,[1–3] regurgitant fractions,[4 5] pressure half-time,[6 7] and colour flow mapping,[8] but none of these methods is load independent and each has its limitations. Even the current reference standard of aortography is dependent on heart rate, blood pressure, and ventricular compliance.

As well as loading conditions, the clinical and haemodynamic consequences of aortic regurgitation also depend upon the size of the regurgitant orifice and this area is theoretically independent of the haemodynamic conditions under which it is measured and thus may be useful clinically. When the valve orifice area in aortic stenosis was calculated non-invasively by the continuity principle it correlated closely with the valve area calculated at cardiac catheterisation by the Gorlin formula.[9–11] In this study, we investigate the feasibility of using the continuity equation in diastole to calculate the aortic regurgitant orifice area non-invasively in patients with aortic regurgitation and to examine the relation between this regurgitant area and the currently used non-invasive measures of the severity of aortic regurgitation.

Patients and methods

STUDY POPULATION

We studied 20 patients with a clinical diagnosis of aortic regurgitation referred for diagnostic echocardiography at Brigham and Women's Hospital in whom the clinical diagnosis of aortic regurgitation was substantiated by cross sectional Doppler echocardiography. Patients with associated aortic stenosis with a peak instantaneous systolic gradient greater than 30 mm Hg were excluded. Patients with atrial fibrillation were also excluded.

DATA ACQUISITION

Cross sectional Doppler echocardiograms were recorded with simultaneous electrocardiography on a Hewlett Packard ultrasonoscope with a 2·5 MHz imaging transducer and a 1·9 MHz Doppler transducer.

Cross sectional echocardiographic images were obtained of (*a*) the left ventricular short axis view at the level of the high papillary muscles from the left parasternal region and the apical four chamber view to calculate left ventricular volumes and left ventricular mass and of (*b*) the left ventricular outflow tract and aorta from the left parasternal region to measure the diameters of the aorta at the level of the annulus and 2 cm above the valve.

Pulsed wave Doppler velocity signals were recorded from the proximal aorta 2 cm above the aortic valve leaflets during diastole from either the apical long axis or the apical five chamber view. The Doppler signals were corrected for the angle of the aorta. Continuous wave Doppler velocity signals of the regurgitant jet were recorded from the left ventricular apex or the second right intercostal space. The highest velocity signal from one of the views was recorded. Doppler colour flow mapping was obtained of (*a*) the left parasternal long axis view of the left ventricle to assess the width of the regurgitant aortic jet at the level of the aortic leaflets and (*b*) the apical left ventricular long axis and the apical five chamber views to assess the length of the regurgitant jet from the aortic valve and the width of the jet at valve level.

DATA ANALYSIS

Doppler velocity signals and two dimensional images were transferred from standard 1·2 mm videotape to the hard disc of an offline computer analysis system (GTI Freeland Medical Division, Indianapolis, Minnesota). For each patient, three consecutive pulsed wave Doppler velocity signals recorded from the supravalvar level (2 cm above the aortic leaflets) in diastole and three continuous wave Doppler velocity signals of the regurgitant jet were digitised to obtain the velocity time integrals, VTI_s and VTI_j respectively, and the mean values for each were calculated.

The cross sectional echocardiographic images of the long axis of the aorta and left ventricular outflow tract from the left parasternal region were digitised. We used a cross-hair electronic cursor to measure the supra-aortic diameter during three consecutive cardiac cycles at the beginning of diastole (that is, concordant with the T wave on the electrocardiogram) 2 cm above the annulus—the point at which the supra-aortic pulsed wave Doppler velocity signals were recorded. We used the leading edge to leading edge convention for these measurements.[12] Mean values for aortic diameter were obtained and used to calculate the supravalvar cross sectional area (A_s), assuming a circular cross section. Blood volume flows were calculated as the product of the velocity-time integrals (VTI) and cross sectional areas (A) of the flow streams. The continuity equation states that flow at the regurgitant orifice equals flow at supravalvar level thus:

$$\text{Aortic regurgitant orifice area } (A_J) \times \text{velocity-time integral } (VTI_J) = \text{supravalvar cross sectional area } (A_s) \times \text{velocity-time integral } (VTI_s)$$

Thus the jet orifice area can be obtained as:

$$A_J = \frac{A_s \times VTI_s}{VTI_J}$$

Two experienced clinical echocardiographers who had no knowledge of the calculated regurgitant areas made an overall Doppler echocardiographic assessment of the aortic regurgitation. This assessment combined the size of the left ventricle, the lengths of the colour flow jets, continuous wave (pressure half time), and pulsed wave Doppler mapping with an overall arbitrary scale from 1 to 5+ (grade 5 was the most severe). The width of the aortic regurgitant jet was also estimated by colour flow mapping at the level of the aortic valve leaflets in the parasternal long axis, the apical long axis, and in the apical five chamber views. The maximal jet widths were measured.

Cross sectional echocardiographic images of the left ventricular short axis at high papillary muscle level and apical four chamber views were digitised. End diastolic and end systolic ventricular volumes, ejection fraction, and left ventricular mass were calculated as previously described.[13 14]

STATISTICAL ANALYSIS

The values of the non-invasive measurements in individual patients were calculated as the means of three consecutive cardiac cycles. Results were reported for the group as mean (SE) and range. The method of Bland and Altman[15] was used to assess the agreement between the regurgitant area method and various non-invasive methods for assessing the severity of aortic regurgitation. In order to do the appropriate calculation, the regurgitant area was also categorised as 1 to 5+ in order to compare with similar numeric grading scale (1 to 5+) in the overall echo score. Univariate analysis by linear regression was used to compare the area with the ventricular volumes. Patients with significant mitral regurgitation (>1+) were excluded from volume and mass correlations.

Results

PATIENTS' CHARACTERISTICS

The mean age of the patients was 55 years (range 22–82 years). There were 12 male and eight female patients. The aetiology of the aortic regurgitation was aortic dissection in one, systemic lupus erythematosus in two, rheumatic disease in six, and unknown in 11. Four patients had mild aortic stenosis (gradients <30 mm Hg), six had mild to moderate mitral regurgitation, and one had mild mitral stenosis and regurgitation. Twelve of the 20 patients were in New York Heart Association class I, six were in class II, and two were in class III failure. Eight out of the 20 patients were on afterload reducing agents when the echocardiography was performed.

ECHOCARDIOGRAPHY

Figure 1 shows representative Doppler signals from one patient. The supravalvar velocity-time integral (fig 1A) obtained in the apical long axis view showed aliasing of the forward blood flow during systole, while regurgitant flow towards the transducer had a peak velocity of 60 cm/s. The velocity declined through diastole as the pressures in the aorta and left ventricle approached each other. The velocity-time integral (VTI) of the regurgitant orifice in the

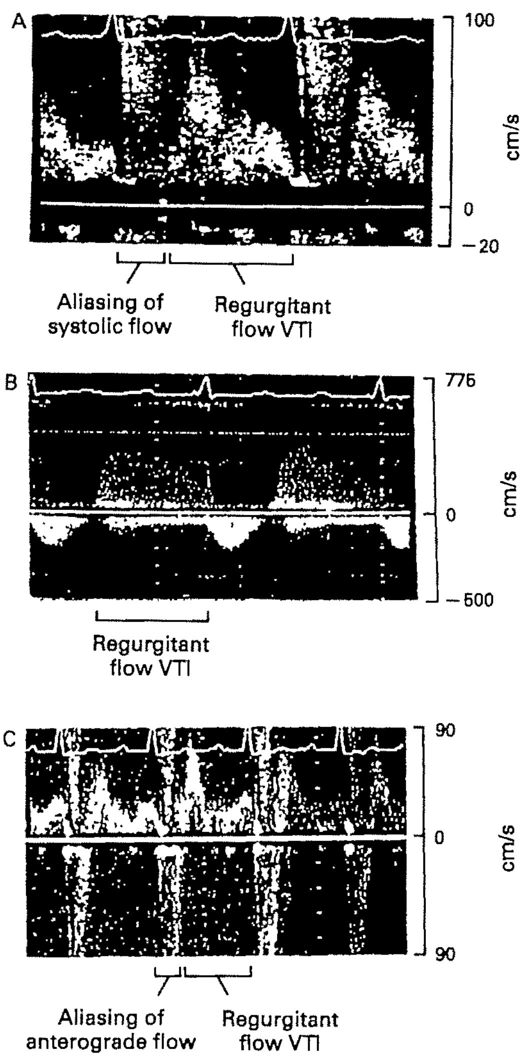

Figure 1 Pulsed and continuous Doppler measurements for calculating the aortic regurgitant orifice of one patient. (A) Pulsed Doppler signal at the supravalvar level obtained from the apical long axis view. (B) Continuous wave Doppler signal at the regurgitant orifice level obtained from the apex. (C) Forward and regurgitant Doppler signals obtained in the aortic arch. The Doppler spectral recordings are plotted with time on the x axis (1 s time lines), velocity on the y axis (calibrations on the right are in cm/s).

Table 1 Mean and range of the aortic regurgitation orifice area and the ventricular volumes/mass

Variable	
AR orifice area (cm^2):	
Mean	0·65 (0·08)
Range	0·25 to 1·73
AR orifice area/annulus area (%):	
Mean	12·7
Range	4 to 26
Maximal proximal jet width (cm):	
Mean	1·1 (0·1)
Range	0·6 to 1·8
End diastolic volume (ml):	
Mean	277 (33)
Range	100 (734)
End systolic volume (ml):	
Mean	141 (22)
Range	46 (424)
Left ventricular mass (g):	
Mean	351 (23)
Range	167 (548)

AR, aortic regurgitation.

same patient was obtained with continuous wave Doppler as shown in fig 1B. The VTI had a well defined border although its decay did not seem to be linear. The peak velocity was approximately 3·5 m/s, and at the end of diastole the velocity was approximately 2·0 m/s. Figure 1C shows the forward and regurgitant flow Doppler signals obtained in the aortic arch by pulsed Doppler. The forward component had a relatively high velocity with aliasing, while the regurgitant component had a peak velocity of 70–80 cm/s.

In these twenty patients, the mean aortic regurgitant orifice area calculated by the continuity equation was 0·65 cm^2 (range 0·25–1·7 cm^2). Overall, the regurgitant orifice area represented from 4 to 26% of the aortic annulus cross sectional area. Table 1 lists the results of various non-invasive measurements. Four patients with mitral regurgitation of >1+ were excluded from volume and mass calculations.

Table 2 shows the results of Bland and Altman analysis. The mean differences between the regurgitant area and the overall echo score was 0·4 with 95% confidence interval of −0·2 to 1·0, though the limits of agreement are large, −2 to +3 grade. The diameter derived from the regurgitant area (assuming a circular orifice, $2\sqrt{\text{area}/\pi}$) agreed well with the maximal jet width with small limits of agreement. However, there was a systematic "overestimation" of 1·0 cm by the colour jet mapping. Table 2 shows that there were wide limits of agreement even between the various non-invasive indices in the same patients.

The end systolic and end diastolic volumes (16 patients) correlated significantly with the regurgitant orifice area, with p values of 0·01 and 0·006 respectively (fig 2). The left ventricular mass did not correlate with the regurgitant orifice area.

Discussion

Non-invasive evaluation of aortic regurgitation has been largely qualitative, which contrasts with the quantitative measurement obtained in aortic stenosis by measuring the pressure gradient and the valve area derived from the continuity equation. The method we describe used the same principle as the calculation of the valve area in aortic stenosis, except that the Doppler velocity-time integrals were measured during diastole.

The regurgitant area measured by the continuity equation method is consistent with the clinical and historical impression that mild

Table 2 Statistical significance of non-invasive indices of aortic regurgitation by the method of Bland and Altman

	Differences (D)	*Standard error (SE)*	*95% CI of D*	*Limits of agreement*
Regurgitant area (1 to 5+) *v* overall echo score (1 to 5+)	0·4	0·3	−0·2 to 1·0	−2 to 3
Regurgitant diameter (cm) *v* colour jet width (cm)	1·0	0·1	0·9 to 1·1	0·5 to 1·5
Overall echo score (1 to 5+) *v* colour jet length (1 to 5+)	−0·6	0·2	−1·0 to 0·2	−2·4 to 1·2
Overall echo score (1 to 5+) *v* pressure 1/2 time (1 to 5+)	−0·4	0·5	−1·3 to 0·6	−4·5 to 3·8

CI, confidence intervals.

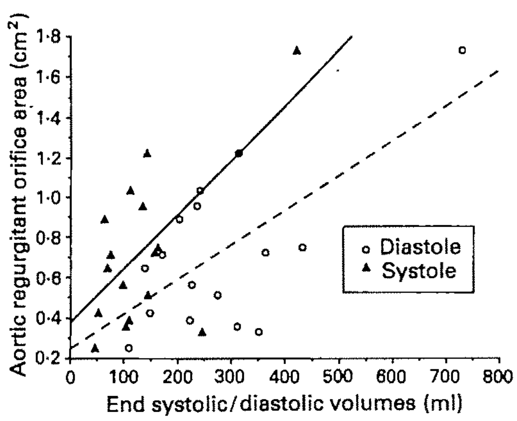

Figure 2 Relation between the aortic regurgitant orifice area and the end systolic (ESV) and end diastolic volumes (EDV) ($n = 16$) (patients with mitral regurgitation excluded). Univariate analysis with linear regression showed a significant correlation between the area and the two volumes (ESV: $r = 0{\cdot}61, p < 0{\cdot}01$; EDV: $r = 0{\cdot}65$, $p < 0{\cdot}006$).

aortic regurgitation is associated with an orifice that occupies 5–10% of the aortic valve, that is 0·2 to 0·5 cm².[16] Severe aortic regurgitation usually results from a regurgitation orifice of more than 20 to 25% of the valve area (that is > 1·0 cm²). These data are consistent with our calculated regurgitant area of 0·25 to 1·7 cm².

Because only four of our study patients required diagnostic cardiac catheterisation, the generally accepted reference standard of cineaortography grading was not available for most patients. However, it is clear that cineaortography is at best semiquantitative, and greatly depends on heart rate, afterload, and ventricular size. As a substitute, we used an overall echo score for comparison. This score is a composite non-invasive measure of the severity of the aortic regurgitation, as assessed by two experienced echocardiographers who were unaware of the calculated regurgitant orifice areas. The regurgitant areas calculated by the continuity equation accorded well with this score, suggesting that this orifice area relates to the overall severity of the aortic insufficiency. The agreement between this regurgitant area and the overall score is no worse than that for other more established indices of aortic regurgitation (that is, the pressure 1/2 time and colour jet length).

The maximal proximal jet width as determined by colour Doppler accorded with the regurgitant area derived diameter obtained by the continuity equation. However, there was consistent overestimation by colour jet mapping. This difference was probably the result of (*a*) the spray effect of the jet,[17] (*b*) the non-perpendicular angle at which the colour Doppler beam bisects the jet, and (*c*) the fact that the area determined by the continuity equation corresponds to the area of the vena contracta and is smaller than the true anatomical regurgitant area.

When patients with clinically important mitral regurgitation were excluded, left ventricular end diastolic and end systolic volumes correlated with aortic regurgitation orifice area. However, there was a degree of variability in these relations because left ventricular volumes depend on both the severity and the chronicity of the regurgitation, and the same holds true for the left ventricular mass.

The advantage of calculating the regurgitant orifice area to determine the severity of aortic regurgitation is that it is theoretically independent of changes in heart rate, pressure gradient, or left ventricular compliance. However, these assumptions will need to be confirmed clinically in a larger study. Regurgitant orifice areas may be useful in several settings: (*a*) in mixed aortic valve disease when the regurgitant orifice area will help to define the aortic regurgitation component of the transvalvar gradient—(thus correcting the underestimation of the stenotic aortic valve area that commonly occurs in non-invasive evaluation of mixed aortic valvar disease), (*b*) in following the patients with chronic aortic regurgitation, in whom the change in orifice area may indicate an insidious increase in severity before the onset of symptoms or a change in left ventricular size and function; (*c*) in aortic regurgitation, when knowing the regurgitant orifice area may provide insight into the mechanism and degree of aortic regurgitation which predictably results in progressive left ventrticular dilatation and decompensation.

LIMITATIONS OF THE STUDY

The assumption that coronary flow makes a negligible contribution to the regurgitation velocity-time integral may artificially slightly increase the regurgitant orifice area. This error is estimated to be of the order of less than 10%. The continuity equation assumes that the supravalvar retrograde flow has a flat velocity profile. It has been shown in an in vitro model that this diastolic velocity profile 2 cm above the valve has a blunted profile as long as the ascending aorta is less than 4·8 cm in diameter.[18] Thus the Doppler signal obtained above the valve should represent the mean diastolic velocity in the aorta and not the increased velocities in the zone of flow convergence. The supravalvar velocity-time integral may be technically difficult to obtain in some patients because of their body habitus. Operators need practice to obtain adequate supravalvar signals.

We demonstrated the feasibility of calculating the regurgitant orifice area non-invasively using the continuity equation and we found that this area agrees with the current non-invasive techniques for assessing the severity of the aortic regurgitation. Further studies are required to define its reproducibility and its relation to the invasive assessment of aortic regurgitation.

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AUDIT

Cost effectiveness of the implantable cardioverter defibrillator: a preliminary analysis

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Abstract

***Background*—An implantable cardioverter defibrillator (ICD) may be effective in reducing the risk of sudden cardiac death. The high cost of ICD treatment, however, compared with alternatives raises the question of whether this new technology is an efficient use of scarce health care resources.**

***Objective*—To estimate the incremental cost effectiveness of the implantable cardioverter defibrillator compared with drug treatment with amiodarone in the management of patients at high risk of sudden cardiac death.**

***Design*—A cost effectiveness model was constructed from data already published and other secondary sources. Differences in patient survival were calculated from life tables for comparable ICD and amiodarone patient series. Costs were based on typical patient management protocols derived from current United Kingdom practice and interviews with physicians.**

***Main outcome measures*—Cost effectiveness of ICD treatment was computed over 20 years; all future costs and effects were discounted at 6% per year.**

***Results*—Estimated life expectancy was 11·1 and 6·7 years with ICD and amiodarone respectively; the discounted 20 year difference lies in the range 1·7 to 3·7 years. Discounted 20 year treatment costs were £28 400 for the ICD and £2300 for amiodarone. Cost effectiveness of ICD treatment lies in the range of £15 400 to £8200 per life-year gained.**

***Conclusions*—Cost effectiveness of ICD treatment is similar to some existing cardiac programmes funded under the NHS but uncertainty exists due to limitations of the data. Costs of ICD treatment may fall in the future as the life of the device increases and less invasive implantation methods are needed. The effectivess of ICD compared with amiodarone is currently being studied by a randomised controlled trial.**

(*Br Heart J* 1992;68:241-5)

The implantable cardioverter defibrillator (ICD) was first implanted into a human patient in 1980[1] and since then it has gained wider use in the management of patients at risk of sudden cardiac death due to ventricular tachycardia (VT) or ventricular fibrillation (VF). In 1990 there were estimated to be over 4000 new implants in the United States[2] whereas the total in the United Kingdom in January 1990 was reported to be 49 devices implanted into 40 patients.[3]

The ICD is an electronic device designed to monitor the heartbeat, recognise VT or VF, and deliver an electric shock (up to 40 joules) to stop the life threatening arrhythmia. Within the generic classification of ICD there are various types, but all consist of a battery powered pulse generator that is implanted in a subcutaneous abdominal pocket and capable of delivering shocks to the heart through two or three electrodes that may be inside or outside the heart.

Use of an ICD is generally considered in patients at high risk of VT, VF and sudden cardiac death, specifically in survivors of sudden cardiac death where electrophysiological study, treadmill, and holter study have failed to identify an effective antiarrhythmic drug. In such patients the main therapeutic alternatives are (*a*) to implant an ICD that will terminate arrhythmias when they occur; (*b*) surgical management such as endocardial resection where an attempt is made to remedy the cause of the arrhythmias; (*c*) empirical drug treatment with amiodarone where the goal is to prevent arrhythmias occurring.

In this study we compare the costs and effects of treatment with ICD versus the alternative amiodarone. Although these are not the only comparisons that could be made they are relevant comparisons that are prevalent in studies examining ICD efficacy.[4 5] The relevance of this comparison is also supported by the existence of a large continuing Canadian randomised controlled trial of amiodarone versus ICD treatment.[6]

As well as the improved efficacy of ICD management is the expectation of higher costs, with the device alone costing about £11 000. Economic evaluation is therefore a necessary and important feature of any overall assessment of this new medical technology: to what extent is ICD treatment a cost-effective addition to the management of patients at risk of sudden death and how does it compare with other cardiac procedures that are competing for scarce health care resources? This study is a preliminary assessment of the economics of ICD treatment in the United Kingdom in which we use the limited published data available to estimate cost effectiveness under various possible outcomes of ICD technology in the near future.

Patients and methods

MORTALITY

No randomised controlled trial of amiodarone versus ICD treatment for patients at high risk of VT or VF has yet been reported. Among the assessments of ICD efficacy, two studies have compared the device with amiodarone. Fogoros *et al* analysed a series of 78 consecutive patients who were eligible for ICD, a third of whom did not receive the device because of temporary unavailability.[4] Although this natural experiment was suggestive of a considerable mortality benefit from ICD compared with amiodarone the results are atypical because the sudden death rate of 31% in the 29 patients taking amiodarone was three times higher than the 9% sudden death rate reported in the largest published series of 462 patients taking this drug.[7] Also a case control study, which is reported in abstract, of ICD versus drug treatment is indicative of ICD mortality benefit, but this is of limited value for the present comparison because only 43% of control patients received amiodarone.

In the absence of reliable data on relative efficacy from a clinical experiment of amiodarone versus ICD, outcomes for our study of cost effectiveness are based upon the largest published patient series for each treatment. Data on survival after ICD implantation were taken from the follow up study of 270 patients by Winkle *et al*[8] in the United States. In this consecutive patient series the mean age was 58 (range 12 to 77) and 80% were men. There was a history of sustained ventricular tachycardia or fibrillation in 96% of patients and 80% had experienced one or more earlier cardiac arrests. Two hundred and sixty nine patients (96%) had experienced at least one failure of antiarrhythmic drug either clinically or at an electrophysiological study, and the average number of drug failures was 3·4 for the entire group.

Data on survival with amiodarone treatment were taken from the follow up study of 462 patients by Herre *et al.*[7] The mean age in this consecutive patient series was 61 and 80% were men. Patients were eligible for amiodarone treatment if they had documented sustained ventricular tachycardia or had experienced cardiac arrest. Before initiation of amiodarone treatment, all patients had experienced failure of at least one antiarrhythmic drug either clinically or at electrophysiological study, and on average there were 2·4 drug failures. These characteristics suggest that many of the patients in the amiodarone series would have been eligible for ICD implantation.

LIFE EXPECTANCY

An assumption of our analysis was that differential patient life expectancy between the treatment groups would be largely a function of differences in rates of sudden cardiac death, because neither treatment is presumed to reduce deaths other than sudden cardiac deaths. Therefore, compared with the amiodarone series, the lower rate of other deaths reported in the ICD series suggests that one or more unknown prognostic factors are unequally distributed between the groups.[7] We have attempted to compensate for this bias by calculating life expectancies with an adjusted all cause mortality where both treatment groups were assumed to have the same non-sudden death rate, this being arbitrarily set to the mean of the non-sudden death rates for the two groups combined for each follow up time. Also for comparison, all life expectancy and cost effectiveness estimates are made with the unadjusted all cause mortality from the published series.

Patient life expectancy is calculated from the adjusted and unadjusted five year mortality series for both treatments by the declining exponential approximation to life expectancy (DEALE) method proposed by Beck *et al.*[9] This method permits declining exponential survival models to be estimated for each five year mortality series, thus enabling forward projections to calculate life expectancies. The DEALE method has been used in previous cardiac studies and the main assumption of the method is that life expectancy approximates to the reciprocal of the annual mortality.[10]

COSTS

For items such as the ICD device and prescription drugs, costs can be based on market prices, but limited data are available on the costs of non-marketed health care items such as ICD implantation surgery; NHS accounting systems do not generate information in a form that can easily be used for the routine costing of specific interventions. Ideally, a detailed prospective costing study of antiarrhythmic treatment would be undertaken, as was done with heart transplantation in the United Kingdom.[11] But the reliability of this method applied to ICD treatment in the United Kingdom might be suspect for two reasons: the small numbers of patients who have received ICDs (49 devices in 40 patients by January 1990[3]) and the rapid changes in ICD technology.

The approach used by us is to combine costs and published data with information from physician interviews to build protocols of resources used for typical ICD and amiodarone patient management in the United Kingdom. Table 1 summarises these protocols. They were costed by two main sources of data: (*a*) national published data on hospital costs and outpatient visits; (*b*) published data from a recent detailed study of costs of various types of cardiac surgery.[12]

The most common method of ICD implantation, left lateral thoracotomy,[3 8] was judged to be between a planned coronary artery bypass graft and an adult closed heart procedure in terms of resource use. It was costed at £3000 exclusive of device generator (£9500) plus leads and patches (£1200). Replacement of the

Table 1 Typical patient management protocols for ICD and amiodarone treatment

	ICD treatment	*Amiodarone treatment*
Initial treatment		
In hospital	1 day intensive care unit, 7–11 days on ward	1 week on ward
Main materials	ICD generator, leads, patches	Amiodarone
Main procedures	Surgical implantation (lateral thoracotomy); EP study to test device after implantation	Further electrophysiological evaluation
Routine follow up		
Hospital visits	Outpatient visit every 3 months; 1 inpatient day every 4 years to replace generator	Outpatient visits every 3 months
Main materials	Device generator replaced every 4 years	Amiodarone (oral) daily (400 mg)
Main procedures	Device interrogation and battery checking (outpatient); device replacement under general anaesthetic (inpatient)	Tests to monitor for drug toxicity

ICD generator, on average every four years, was costed as equivalent to a pacemaker replacement (£750)[12] and added to this are the costs of routine three-monthly follow ups for device and battery checks.

Consistent with the patient series of Winkle *et al*[8] it was assumed that 23% of patients with an ICD would also be taking amiodarone. Patients receiving only amiodarone were assumed to spend one week in hospital for a loading dose of the drug and further EP evaluation (£1050) then an oral daily dose of 400 mg in each subsequent year (£223 per year) with outpatient visits to monitor for toxicity every three months (£80 per year).

Given limitations of the data the cost analysis contains several simplifying assumptions. For example, no explicit additional costs are incorporated into the amiodarone treatment group for management of recurrence of arrhythmia, drug intolerance, or discontinuation of the drug. These costs will be at least partly offset by additional costs in the ICD group for the management of complications such as infections and false shocks.

COST EFFECTIVENESS

The purpose of the analysis of cost effectiveness is to determine at what extra cost the extra life-years of patient benefit result from ICD implantation. All analyses are relative to the alternative of amiodarone treatment, and therefore the cost effectiveness of ICD treatment is the ratio of the net cost of ICD treatment (ICD total costs minus amiodarone total costs) to the net benefits measured as life-years gained (or lost).

Given that costs and benefits occur at different times in the future it is necessary to discount the future trends into present values. The need to discount in economic appraisal merely reflects the fact that individuals have a positive rate of time preference and prefer benefits sooner and costs later.[13] The discount rate used is 6% per annum as recommended by Her Majesty's Treasury for public sector appraisals.

Sensitivity analysis was performed on several variables where limited data were available and uncertainty exists. The purpose of sensitivity analysis is to explore the extent to which the estimated cost effectiveness results stand up to alternative estimates and assumptions conerning key variables. We conducted a two way analysis of sensitivity: (*a*) by mortality series, adjusted versus unadjusted; (*b*) by alternative assumptions about future treatment and costs. Whereas some alternative assumptions are based on present trends in management (for example reduced follow up times and increased generator life) others, such as the possible reduction in the price of the device due to increased market competition, are more speculative.

Results

Table 2 shows the five year mortality data for ICD and amiodarone treatment. At five years the sudden and non-sudden death rates for ICD treatment were 4·4% and 21·8% respectively, with comparative amiodarone death rates of 21% and 41%. Adjusted all cause five year mortality for ICD treatment was estimated to be 35·8% (this being 4·4 + ((21·8 + 41·0)/2)) and 52·4% for amiodarone.

In table 3 life expectancy with ICD is estimated for the adjusted mortality series to be 11·1 years and 6·7 years with amiodarone. The difference in life expectancies discounted at 6% is 2·3 years in favour of ICD. Overall, in the 20 year period of the projected costs and benefits of the study, a range of 1·7 to 3·7 discounted life years would be gained from ICD treatment.

Table 4 shows total cost and cost effectiveness data. For the adjusted mortality series the total discounted cost of ICD treatment over 20 years is £28 400 compared with £2300 for amio-

Table 2 Mortality data for ICD and amiodarone treatment

	ICD treatment (Winkle et al,[8] n = 270)/amiodarone treatment (Herre et al,[7] n = 462)				
Follow up year	*% Sudden deaths*	*% Non-sudden deaths*	*% All cause deaths*	*Mean % Non-sudden deaths**	*% Adjusted all cause deaths*
1	0·9/ 9·0	6·8/15·0	7·7/24·0	10·9	11·8/19·9
3	4·4/15·0	14 0/28 0	18·4/43·0	21·0	25·4/36·0
5	4·4/21·0	21·8/41·0	26·2/62·0	31·4	35·8/52·4

*The mean non-sudden death rate for the two groups combined at each follow up time is added to the sudden death rate to derive the adjusted all cause death rate.

Table 3 Declining exponential approximation of life expectancy and discounted life-years gained from ICD treatment

	Adjusted mortality		*Unadjusted mortality*	
	ICD	*Amiodarone*	*ICD*	*Amiodarone*
Mean annual mortality rate (m)	0·09	0·15	0·06	0·19
Life expectancy (l/m)	11·10	6·67	16·60	5·30
Life expectancy discounted at 6% per year	7·9	5·6	10·1	4·2
Total discounted life-years gained from ICD	2·3	—	5·9	—
Discounted life-years gained from ICD in 20 years	1·7	—	3·7	—

For the adjusted ICD mortality series the cumulative proportion surviving, S(t), to t = 5 years (0·64 from table 2) is determined by S(t) = exp(−mt) where m = 0·09 and t = 5.

darone, giving a net cost of £26 100 for ICD treatment. Taking the ratio of the net cost of ICD treatment to the net benefit (1·7 discounted life-years) gives the cost effectiveness of ICD therapy as £15 400 per life-year gained. The same calculations for the unadjusted survival series show a much lower cost effectiveness ratio of £8200 per life-year gained.

The sensitivity analysis in table 5 shows that cost effectiveness calculations are most sensitive to alternative estimates of patient survival, being £15 400 per life year gained for the mortality series adjusted for between study differences in non-sudden death rates and £8200 for the unadjusted mortality data. Analysis by alternative treatment assumptions for each mortality series suggests that reductions in the fixed "start up" costs of treatment due to initial ICD implantation will generate a modest improvement in cost effectiveness (£14 590 per life-year, adjusted series) when compared with reductions in recurrent cost due to factors such as increased life expectancy of the device from four to six years (£12 297 per life-year).

Discussion

In a recent editorial Campbell concluded that the implantable defibrillator is an effective treatment for those at risk of sudden cardiac death and that cost is the main constraint upon the wider use of this treatment in the United Kingdom.[14] Cost effectiveness analysis offers a standardised framework for assessing and combining costs and effects to permit comparison between new and existing treatments competing for limited resources.

Table 4 Costs, effects, and cost-effectiveness of ICD treatment

	Adjusted mortality	*Unadjusted mortality*
Total discounted cost to 20 years:		
ICD treatment	£28 400	£32 300
Amiodarone treatment	£2300	£2100
Net cost of ICD treatment	£26 100	£30 200
Net effectiveness of ICD	1·7 life-years	3·7 life-years
Net cost effectiveness of ICD	£15 400 per LYG	£8200 per LYG

Cost effectiveness is calculated as the ratio of net cost to net effectiveness for each mortality series. LYG, life-years gained.

Table 5 Sensitivity analysis of cost effectiveness estimates

	Cost per life-year gained (£)	
	Adjusted mortality	*Unadjusted mortality*
Base estimate	15 400	8200
Cost of ICD implantation surgery reduced by 50% to £1500	14 590	7769
Device generator price reduced by 20% to £7600	13 029	6890
Average generator life increased from 4 to 6 years	12 297	6384
Follow up frequency reduced from 3 monthly to 6 monthly	14 776	7784
Amiodarone management costs increased by £1000 per year	12 954	7221

Our study shows that, compared with management with amiodarone, the cost effectiveness of ICD treatment lies in the range £8200 to £15 400 per life-year gained. How should such cost effectiveness data be interpreted? A common and illuminating approach is to compare the results from this study with other cardiac treatment interventions to find out whether the cost per unit outcome from ICD treatment is greater or less than other treatments that are funded through the NHS. Whereas some cardiac interventions such as heart transplantation generate life-years at lower cost than ICDs (£5000 per quality adjusted life year, 1985 prices) some interventions are nearly equivalent or worse than ICD treatment, such as coronary bypass grafting for moderate angina with one vessel disease (£12 000 per quality adjusted life-year)[15] and drug treatment (in addition to diet) for lowering blood cholesterol to reduce coronary mortality (£19 000 per quality adjusted life year).[16]

Sensitivity analysis indicates that the main source of variation in estimates of cost effectiveness relates to uncertainty about the size of the mortality benefit attributable to ICD treatment. In our study this uncertainty is due, in part, to questions of comparability of the ICD and amiodarone series and the extent to which the mortality data can be generalised to other patient groups. For example, recent smaller series have reported somewhat higher survival with amiodarone,[17 18] and with ICD.[19] Economic evaluation ultimately depends on the strength of the epidemiological evidence on which it is based, and for this reason more precise estimates of size of the effects of ICD treatment from randomised controlled trials, or (at least) well organised registries,[20] would be valuable.

Present estimates of cost should be viewed in the context of the rapid technological innovation surrounding the ICD device and its implantation. Such problems are commonplace in assessments of new technologies.[21] At least, evaluation studies should be designed to recognise the dynamic nature of the technology and attempt to quantify the impact of possible future trends in a sensitivity analysis. In the specific case of ICDs there are three reasons why costs of ICD treatment are likely to fall in the future:

(*a*) The next generation of ICD devices are expected to have much longer lives (possibly up to nine years) and have capacitors that reform automatically thus reducing the need for

frequent maintenance or device replacement;
(*b*) Advances in methods for implanting defibrillators may result in current surgical techniques of lateral thoracotomy and median sternotomy being superseded by less invasive transvenous methods with an expectation of lower costs and risks;
(*c*) More widespread use of the devices and variation in device types may serve to promote price competition between manufacturers.

The validity of the estimates presented in our study is difficult to determine. One approach is to examine the extent to which our estimates are consistent or convergent with other studies. In a recent study in the United States Kupperman *et al*[22] estimated a cost effectiveness range for ICD versus drug treatment of US$15 600 to $29 600 per life-year gained, deriving cost data primarily from 1984 Medicare claims and survival estimates from publications before the major reports used here. An Australian technology assessment report on ICDs has also appeared and ICD cost effectiveness is estimated to range from AU$17 850 to AU$35 800 per life year, where ICD is assumed to be used only after electrophysiological testing has failed to find an effective antiarrhythmic agent.[23] Results from our study are therefore consistent with other published studies and very similar in estimates of cost effectiveness.

A limitation of existing economic appraisals is the exclusion of effects that antiarrhythmic treatments may have upon patients' health related quality of life. To measure treatment benefits only in terms of life extension is to bias comparison against those treatments that have higher mortality but may maintain or improve quality of life, either through the relief of symptoms or the avoidance of adverse effects. Some follow up studies on ICD patients have explored physical and psychological effects but no prospective controlled comparative studies have yet been published.[24-26] Quality of life data, however, are being collected as part of the Canadian implantable defibrillator study[6] (a randomised controlled trial of ICD versus amiodarone) with a variety of measures including the Nottingham Health Profile[27] and the Mental Health Inventory[28] to assess psychological wellbeing.

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VIEWS FROM THE PAST

Walter Hayle Walshe (1812–1892) and his book *Diseases of the Heart*

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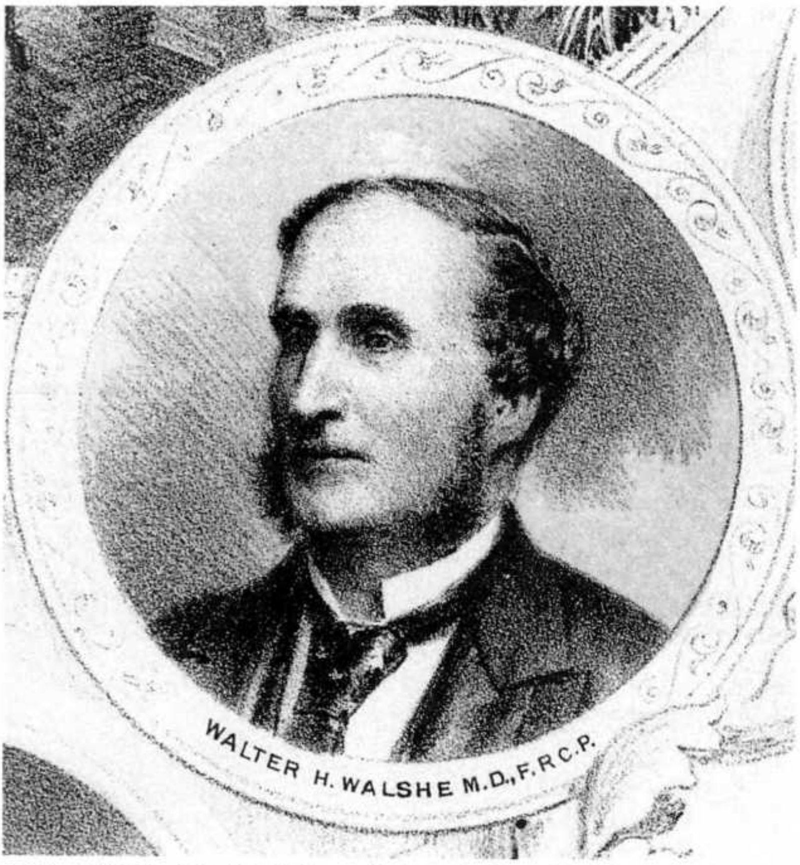
Walter Hayle Walshe distinguished physician, author, and scholar, contemporary of Queen Victoria (1819–1901) and Charles Dickens (1812–1870) is one of the neglected forerunners of the great British cardiologists of the early twentieth century. His unconventional and peripatetic undergraduate days, followed by academic pre-eminence and rounded off by an extended, varied, and rewarding retirement, make Walshe an individual worthy to be rescued from oblivion. His *Diseases of the Heart*, which first appeared in 1851 and reached the peak of popularity with the fourth edition published in 1873, deserves to rank with the works of James Hope, William Stokes, and Austin Flint as the important cardiology texts of the pre-Mackenzie era.

Walter Hayle Walshe

Walter Hayle Walshe was born in Dublin on the 19 March, 1812. His father was a successful barrister who died aged 48. In 1827 Walter entered Trinity College, the ancient institution founded during the reign of Queen Elizabeth I, with the intention of following his father's career. In 1830 he joined his mother who had moved to Paris after the death of her husband. These were exciting times with the July revolution leading to the abdication of Charles X and the succession of Louis Philippe as constitutional monarch.

In Paris the 18 year old enrolled at the Sorbonne and studied Classical, Arabic, and Oriental languages, subjects that remained lifelong interests. In 1832, possibly influenced by the great cholera epidemic which in one month, April, claimed more than 13 000 lives, he decided to change faculties and enrolled in biological sciences. Paris, at the time, was one of the progressive centres of medical learning, stimulated by the discoveries and teachings of Jean Nicolas Corvisart and Hyacinth Laennec. Walshe's teachers included the surgeon Baron Guillaume Dupuytren to whom he was apprenticed as surgical dresser contemporaneously with Oliver Wendell Holmes. He served his medical clerkship at the Hotel Dieu and attended ward rounds at La Charite. In 1834 he joined the service of the master clinician Phillipe Charles Alexandre Louis at La Pitie. He was introduced to a new scientific and statistical approach to medical diagnosis and treatment and embraced the need for the detailed appraisal of all relevant clinical observations. The application of these methods to the study of diseases such as phthisis and enteric fever led to a better understanding of their cause, management, and outcome.

Intending to take his medical degree in an English-speaking institution, Walshe, in 1835, moved to Edinburgh and graduated from that university in the following year. He returned to Paris for a brief period but in 1838 settled in the north of London to take up general practice. His main interest remained the study of pathology and scientific investigation of medical problems. In the next two years he became a prolific writer contributing original observations on diverse subjects including malignant disease, pulmonary tuberculosis, empyema, and subdural haematoma. His articles attracted attention and led to his appointment, in 1841 at the age of 29 years, as Professor of Morbid Anatomy at University College London, in succession to Sir Robert


WALTER H. WALSHE M.D., F.R.C.P.

Walter H Walshe, MD, FRCP. From a Lithograph: Memorial of University College Hospital by H Hall, by courtesy and with permission of the Wellcome Institute Library, London.

Carswell. There he was not only part of a strong medical team but also maintained a lively interest in the activities of the faculty of Arts. In 1846 he was appointed Holme Professor of Clinical Medicine and became physician at University College and Brompton Hospital for Diseases of the Chest. Two years later he reached the pinnacle of his academic career when he took up the position of Professor of the Principles and Practice of Medicine succeeding C J B Williams. In absolute charge of medical teaching at University College Hospital he delivered "clinical lectures" as well as the "systematic course".

Walshe proved to be a gifted and meticulous teacher. His lectures and articles were based on carefully recorded personal experiences and a thorough knowledge of the literature. Facts were presented on the basis of numerical and statistical details and conclusions arrived at by a process of logical deduction and exclusion. His students appreciated and admired his ability to simplify complex concepts by presenting the core and essentials of the problem under discussion.

Walshe retired from his academic duties in 1862, at the early age of 50 years, to be succeeded by Sir William Jenner. He had attained an international reputation and membership of medical societies in Paris, Copenhagen, and Athens. He became a successful consultant physician and was in great demand as an expert witness in medico-legal disputes, putting to good use his legal training. He married late in life and devoted the last decade to publishing books on subjects not related to medical practice but amplifying experiences gained during his early years at the Sorbonne, such as *Dramatic Singing Physiologically Estimated* (1881) and *The Colloquial Linguistic Faculty and its Physiological Groundwork* (1885). A revealing and moving comment on Walshe's final years was published by a colleague: "That his exquisitely sensitive nature under the influence of physical pain, was apt to take a materialistic and pessimistic view of things must be well known to his friends, but this was but a symptom of his suffering".[1]

Anticipating the discovery of myxomatous, billowing mitral valve by a century, Walshe wrote "may it be that defect in the elastic tissue, which seems to have been shown by W O Markham to exist in the valves, allows their eversion into the auricle". It is of interest that W O Markham, assistant physician to St Mary's Hospital, published in 1853 a translation of the 1850 fourth edition of Joseph Skoda's *A Treatise on Auscultation and Percussion*. Who then, first described mitral valve prolapse?

Diseases of the Heart

The book *A Practical Treatise on Diseases of the Heart and Lungs, including the Principles of Physical Diagnosis* was published in 1851 and dedicated to Walshe's teacher P C A Louis. A second edition followed in 1856 (thereafter the book was divided into two parts) the third edition devoted to diseases of the heart appeared in 1862, and the fourth and last in 1873.

Walshe's book rapidly gained the reputation of being "one of the most careful and elaborate epitomes of knowledge in the matters with which it deals".[2] The foreword to the fourth edition contained prophetic words when it mentioned "medical and surgical means of successfully controlling the progress of structural diseases of the heart and great vessels".

Part I deals in detail with the clinical examination of the heart and blood vessels under the traditional headings of inspection, palpation ("application of the hand"), percussion, and auscultation. Percussion and auscultation were clearly inspired by Leopold Auenbrugger, whose writings on percussion were rescued from obscurity by Corvisart's translation from German to French and by Laennec, the inventor of indirect auscultation: both were dominant personalities during the first half of the nineteenth century.

Walshe's description of the physical signs and pathological findings in valvar heart disease was the result of close observation rounded off with personal speculation. He was one of the first to stress the presystolic timing of the thrill and murmur of mitral stenosis and he noted that the impulse may be regular or irregular in force or rhythm and, being unaware of the existence of atrial fibrillation, he wrote "in all probability the irregularity when present is in the main neurotic". He stated that in patients with mitral regurgitation a systolic thrill may sometimes be felt "at or about the left apex . . ., but the essentially distinctive sign of this regurgitation is a systolic left apex murmur".

He described the post-mortem demonstration of mitral regurgitation: "Tie the aorta and coronary arteries, cut off the apex of the heart and let fall against the mitral valve a full-sized column of water; the valve will either support the water or allow it to pass through to the auricle. If the whole of the ventricle above the floor formed by the valve remains filled with water, scarcely a drop filtering through, there can be no doubt the valve was competent during life."

Part II discusses individual conditions under the headings of dynamic and organic diseases. Walshe described Heberden's angina pectoris as a rare affection, but pseudo-angina "a condition which I almost daily meet." More akin to present-day concepts are the statements: "The cardinal fact in the prognosis of real angina under any circumstances is its incertainty", and "Has Angina Pectoris any anatomical character? In all the cases I have opened there was more or less calcification with contraction of the coronary arteries."

He recorded small contracted pupils in patients with aneurysms of the arch of the aorta, no doubt referring to Argyll Robertson pupils of syphilitic heart disease. He described in detail the examination of coarctation of the aorta: "Not the least important and readily ascertainable of the physical signs are presented by the extreme pulsations of the carotid, subclavian, temporal, deep cervical (? common carotid) and intercostal arteries. Occasionally local expansile impulses aneurismal to the feel but sometimes strong enough to gradually wear away the ribs, may be felt from place to place in the latter vessels". An illustration of the collateral arterial circulation produced but unpublished by his predecessor Carswell appears in the book.

How does Walshe's work compare with that of his predecessors and contemporaries?

James Hope, eleven years his senior, was a brilliant experimental physiologist whose career was cut short by his premature death due to pulmonary tuberculosis. His contributions to the understanding of valve incompetence and heart failure, based on animal work, remain milestones in the history of cardiology. Hope was innovative while Walshe was more inclined towards meticulous observation and detailed analysis. Octavius Sturges, writing in the *Lancet* summarised the views held at the time of Walshe's death: "He differs from Stokes and from Sibson occasionally and with much respect, from Skoda more often and not unwillingly, from Hope always and with joy".[3]

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LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

Management of patients with Björk-Shiley prosthetic valves

Sir,—In his editorial[1] Mr Tom Treasure correctly describes the development of the Björk-Shiley prosthesis—from the Delrin disc valve to the spherical disc valve, to the convexo-concave valve with an opening angle of 60° (CC60), to the convexo-concave valve with an opening angle of 70° (CC70), and finally to the Monostrut valve that is manufactured without any welding procedures. He also mentions that the risk for outflow strut fracture seems limited to the CC60 and CC70 models, with the highest risk in some CC70 valves. He claims that the operative risk for elective replacement of these valves might be as high as 16% for mitral valves and 9% for aortic valves and argues that prophylactic replacement of these valves (making no distinction between CC60 and CC70 valves) "for fear alone is unjustifiable".

Certainly, replacement of these valves should not be done "for fear alone", but should be done after a careful assessment of the risk for strut fracture and the risk of a prophylactic reoperation. Unfortunately, I cannot agree with Mr Treasure's conclusions, but believe that some patients with CC70 valves would benefit from elective replacement of their valves on the following grounds.

In 1986 we published the long-term results of valve replacement with the Björk-Shiley prosthesis[2] and in 1989 we presented an updated follow-up on those with CC60 and CC70 valves.[3] Our original report included 3334 Björk-Shiley valves (of which 884 were CC60 and 577 were CC70 valves) followed for 17 511 years (mean follow up 6·3 years). Our updated follow-up included 8299 patient-years for CC60 and CC70 valves. The follow up was 99% and the necropsy rate was 75%. These are the largest series of Björk-Shiley valves followed for an extended time, and unfortunately also the largest single-institution experience with Björk-Shiley valve fractures. Neither of these reports were referenced by Mr Treasure.[1] In our original report we found a constant, but similarly low risk of strut fracture in the CC60 valves (constant hazard function). The risk in CC70 valves was considerably higher, although it seemed that this high risk decreased over the years (decreasing hazard function). However, in our more recent report it was clear that this apparent decrease in the risk of strut fracture was an artefact and that the risk among the large (that is, 29–33 mm), early CC70 valves (so-called group I valves[4]) remained almost constant over a seven year follow up. Furthermore, and contrary to Mr Treasure's comments, this was not limited to mitral valves. The seven year actuarial incidence of strut fracture among large aortic CC70 valves was 15·3% and that for large mitral CC70 valves was 11·3%. This corresponds to a yearly incidence of strut fracture of 1·8–2·0%. These findings have recently been corroborated in an international multicentre study including 20% of all CC70 valves implanted worldwide.[5] In this study it was found that a 29–33 mm diameter was the only risk factor for strut fracture in CC70 valves. There was no difference between aortic and mitral valves.

Also we do not believe that prophylactic valve replacement entails such a high operative risk as proposed by Mr Treasure. As he correctly points out, the re-replacements in the United Kingdom's Cardiac Surgical Register includes all patients undergoing valve re-replacement, irrespective of the cause, and most of these patients probably had severe symptoms. Prophylactic re-replacement in highly selected patients would carry a much lower risk. In our own, albeit small, experience of prophylactic or incidental replacement 30 day mortality was one in 27 patients (3·7%). This was a 72 year old woman who underwent incidental replacement of her large CC70 mitral prosthesis together with aortic valve replacement for symptomatic aortic stenosis. Also two fairly large series of prophylactic replacements of aortic Braunwald-Cutter prostheses have been reported, with early mortality less than 3%. These procedures were performed when methods for intraoperative myocardial protection were much less developed than they are today.[6,7]

I believe that there is strong statistical support for prophylactic replacement of some of the large (29–33 mm) CC70 valves, whether in the aortic or the mitral position.

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1 Treasure T. Management of patients with Björk-Shiley prosthetic valves. *Br Heart J* 1991;66:333–4.
2 Lindblom D, Björk VO, Semb BKH. Mechanical failure of the Björk-Shiley valve. Incidence, clinical presentation, and management. *J Thorac Cardiovasc Surg* 1986;92:894–907.
3 Lindblom D, Rodriguez L, Björk VO. Mechanical failure of the Björk-Shiley valve. Updated follow-up and considerations on prophylactic rereplacement. *J Thorac Cardiovasc Surg* 1989;97:95–7.
4 Ostermeyer J, Horstkotte D, Bennett J, *et al.* The Björk-Shiley 70 degree convexo-concave prosthesis strut fracture problem (present state of information). *Thorac Cardiovasc Surg* 1987;35:71–7.
5 Ericsson A, Lindblom D, Semb G, *et al.* Strut fracture with the Björk-Shiley 70 degree Convexo-concave valve: an international multi-institutional follow-up study. *Eur J Cardiothorac Surg* 1992;6:339–46.
6 Pluth JR. Discussion of Sandza JG Jr, *et al*: Replacement of prosthetic heart valves. A fifteen-year experience. *J Thorac Cardiovasc Surg* 1977;74:864–74.
7 Wideman FE, Blackstone EH, Kirklin JW, Karp RB, Kouchoukos NT, Pacifico AD. Hospital mortality of re-replacement of the aortic valve incremental risk factors. *J Thorac Cardiovasc Surg* 1981;82:692–8.

This letter was shown to the author, who replies as follows:

Sir,—I am grateful to Dr Lindblom for his response which may help us towards a rational approach to the question of elective reoperation to replace Björk-Shiley heart valves that are known to be at risk of strut fracture.

He draws to our attention his own publications that I did not cite directly in the editorial. The data to which he refers, from Björk and colleagues, were included amongst the six clinical series that comprised the data base of the multi-institutional advisory panel.[1] I apologise for any offence this has caused but the other five series in the panel's meta-analysis were not individually cited either. What is perhaps more important is to draw readers' attention to the new data contained in the retrospective cohort study of 2303 patients with convexo-concave (CC) valves in The Netherlands.[2] For large mitral (≥29 mm) 70°CC valves the risk of strut fracture is over 2% per annum. Valves of 27 mm or less in the 60°CC pattern were not liable to fracture. There were some discrepancies between the Dutch and Swedish results with the mitral prostheses being much more at risk than the aortic ones in Holland, but the authors warned that with a 25% necropsy rate there must be an overall underestimate of strut fracture. In my article I seemed to emphasise the mitral valve, but only because fewer patients have aortic prostheses ≥29 mm. In fact they represent 5·3% of all Björk-Shiley aortic valve replacements in the UK Heart Valve Registry.[3]

I quoted data from the United Kingdom Cardiac Surgery Register for mortality with reoperation and Dr Lindblom questions this, reiterating my own caveat, that emergency reoperation and endocarditis were included and this may exaggerate the true risk for selected, elective re-replacement. However, in challenging the use of these data he illustrates the two reasons why I believe we should quote registry data whenever possible for discussions of this type, rather than quoting selected series. First he tells us that his group have lost only one out of 27 cases with a risk of under 4%. The 95% confidence interval is 0·1% to 19% for mortality and even if we follow Kirklin and take the more lenient 70% confidence interval the upper limit is 13%. We cannot be sure that his excellent results represent a true low risk rather than a lucky run. He then quotes the University of Alabama experience in replacement of Braunwald-Cutter aortic valves in which the mortality was 1/65 in a series of operations performed by Kirklin, Karp, Kouchoukos, and Pacifico.[4] It is possible that not all groups will be able to emulate these results.

The operative risk that patients face is that in the centre to which they are referred and if that is estimated, on the basis of registry or audit data, to be less than the risk of death from strut fracture then prophylactic replacement may be considered. Some patients may find intolerable the knowledge that they have within them a valve that may fracture at any time, and in such patients an operation would be justified. That is a very real issue but must be distinguished from a cold analysis of numerical risk.

As far as numerical risk is concerned it seems justifiable to offer elective operation to selected groups as both Lindblom and van der Graaf[2] have suggested. Those most at risk are patients with large (≥29) 70°CC valves. Those who have most to gain are the younger patients with good cardiac status for whom median survival after valve replacement is in excess of 15 years. For them risk of an elective re-replacement in experienced hands is significantly less than the cumulative risk of strut fracture during their expected lifetime.

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1 Hiratzka LF, Kouchoukos NT, Grunkemeier GL, Miller DC, Scully HE, Wechsler AS. Outlet strut fracture of the Björk-Shiley 60° convexo-concave valve: current information and recommendations for patient care. *J Am Coll Cardiol* 1988;11:1130–7.
2 van der Graaf Y, de Waard F, van Herwerden LA, Defauw J. Risk of strut fracture of Björk-Shiley valves. *Lancet* 1992;339:257–61.
3 Taylor KM, Livingstone S. Personal communication from the United Kingdom Heart Valve Registry.
4 Wideman FE, Blackstone EH, Kirklin JW, Karp RB, Kouchoukos NT, Pacifico AD. Hospital mortality for re-replacement of the aortic valve. *J Thorac Cardiovasc Surg* 1981;82: 692–8.

Abnormal right heart filling after cardiac surgery

Sir,—Dr Wranne and colleagues demonstrated in figure 5 of their interesting study that the lateral aspects of the tricuspid annulus showed a more pronounced motion loss after cardiac surgery than those of the mitral annulus.[1] As one of the possible explanations they suggested that the left ventricle was better preserved during surgery than the right ventricle. This theory is confirmed by an experimental study of the tissue electrolyte content in the right and left ventricular myocardium after normothermic open heart surgery in dogs.[2] Cardiac arrest had been induced (*a*) by clamping the ascending aorta, (*b*) by aortic clamping with additional injection of a cardioplegic solution, (*c*) and by electrically induced fibrillation (with preservation of the coronary circulation). Tissue electrolyte content was determined before extracorporeal circulation was started, as well as after an hour of recovery from a cardiac arrest of 30 or 45 minutes. In all these forms of cardiac arrest, tissue water had increased and potassium and magnesium decreased. These changes were more pronounced in the myocardium of the right ventricle in all experimental groups. A decrease in potassium and magnesium content in tissue is an indicator of cellular injury.[3-5] In the study in dogs the loss of these electrolytes was more pronounced in the myocardium of dogs with low cardiac output than in animals with adequate circulation after cardiac arrest. Because the dogs did not have genuine cardiac surgery cardiac arrest was relatively short and hypothermy was not used. Hence we do not believe that the observed differences between the ventricles were predominantly caused by a mechanical impediment, more pronounced exposure of the right ventricle to room temperature, or heat radiated from the operating room lights, as suggested by Wranne *et al.* We attribute this phenomenon to a proposed difference in the susceptibility of the right and left ventricular myocardium to systemic disturbances, as it has been described for various diseases, such as hyperosmolar coma or liver failure.[3 4 6] Histologically, ultrastructurally, and biochemically, the right ventricular myocardium differs from that of the left ventricle.[4 6 7] According to Doerr the different susceptibility of the ventricles to disease can be explained by phylogenesis: the right ventricle belongs mainly to the priscomyocardium and is phylogenetically older than the left ventricular neomyocardium.[6] Perhaps this so-called "theory of pathoclisis" also explains the differences between the right and left ventricular function seen after cardiac surgery and described by Wranne *et al.*

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1 Wranne B, Pinto FJ, Hammarström E, St Goar FG, Puryear J, Popp RL. Abnormal right heart filling after cardiac surgery: time course and mechanisms. *Br Heart J* 1991;66:435–42.
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3 Brandt G, Thierauf P, Metze K. Postmortale Diagnostik von Elektrolytentgleisungen mit Hilfe der Gesamtgewebsmineralanalyse. In: Jellinger K, Gross H, eds. *Current topics in neuropathology*. Vol 5. Vienna: Facultas-Verlag, 1978:15–21.
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Working party report on cardiac rehabilitation

Sir,—I was most interested to read the report from the working party on coronary rehabilitation and would like to congratulate them on their obvious hard work.[1]

Because coronary rehabilitation has not been a high technology subject it has lapsed into a cinderella type of service with a few enthusiastic doctors and many more enthusiastic nurses, physiotherapists, and occupational therapists soldiering on in isolation. It is for this reason that research has not been very forthcoming because individual units find that they do not have enough patients to produce meaningful controlled trials: for example, the trial by a Glasgow team in 1991 in the end had 12 patients in the treatment group and 10 in the control.[2]

Up to now it is the paper from O'Connor *et al* in 1989, which provided an overview of 22 small trials, that has allowed us to believe that coronary rehabilitation had a part to play in the treatment of acute myocardial infarction.[3]

Your readers may be interested to know that here in the North-West we have had the Coronary Rehabilitation Development Organisation (CReDO) for about two years now. It is a loose knit confederation of just such enthusiasts as I have described who meet quarterly to exchange ideas and support others who are in the process of setting up a rehabilitation programme.

Three things have become apparent. Firstly it requires a dedicated nurse/physiotherapist/occupational therapist around whom the whole programme pivots; secondly, it does not need much money to set up a simple scheme; and thirdly, and probably the most important, any scheme to be successful needs the wholehearted support of the consultant in charge of cardiology for that district—whether cardiologist or general physician with an interest in cardiology.

A meeting is to be held on 26 September 1992 in Oxford to try to organise a national association that may well then allow us to produce some proper scientific evidence to persuade those who control the budgets that rehabilitation is a worthwhile and cost-effective part of the treatment of myocardial infarction.

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BOOK REVIEWS

Heart disease: A textbook of cardiovascular medicine. 4th ed. Edited by Eugene Braunwald. (Pp 1874; $119.) Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: W B Saunders Company, 1992. ISBN 0-7216-3097-9.

When the original edition of this comprehensive textbook appeared, I was given the opportunity to review it in 1980. It was the first of a new generation of such works, and set the standards by which others might be judged. Not only did other important similar works respond by improving their quality but a number of other textbooks have appeared, mainly in the United States though with one British based offering.

As with previous editions, Braunwald is an author or co-author of many of the chapters as well as having orchestrated the whole. He has taken considerable trouble to ensure that what appears is up to date even at the cost of shedding some earlier references from some chapters that may be of historical relevance. But as his purpose is to present contemporary evidence, this has enabled him to limit the size to some extent. Nevertheless, there are still 1874 pages of text and illustrations, with ample and appropriate references.

The whole of the subject is covered extensively and if some miss their favourite topics, that will be highly exceptional. For a description of pathological processes generally one will have to turn elsewhere and this is probably appropriate in a book aimed at providing clinically relevant information, yet readers should not forget the potential importance of such knowledge.

There have been modest changes in authorship once again between the third and fourth editions, and Braunwald's system of having all the chapters externally reviewed ensures a high standard throughout.

The most striking feature of the present edition is the lavish use of colour. Generally this is helpful and indeed to have the chapter numbers coloured red discriminates them from the pages above and makes for the easier finding of what one needs from an index that did not fail several random tests. Those interested in electrocardiography will, however, question the use of red for the tracings and a dark but absolutely crisp background for the grids (the latter is an excellent feature); surely it would have been easier for most if the conventions had been observed and the tracings had been dark and the background coloured as you see in clinical tracings. In other respects I accept, and on the whole welcome, the use of colour, which enables one to pick out relevant parts of illustrations more easily.

Once again, Braunwald and his contributors have provided us with a standard reference book on cardiology superior to its competitors and essential for those who want up to date information properly presented and well argued. The size of the book cannot be criticised because it reflects the scope of the specialty. I have previously found the two volume version easier to handle and suspect that others will also find this so with the fourth edition. My minor caveats do not detract from my conclusion that the fourth edition is excellent and up to date.

DENNIS M KRIKLER

Atrial fibrillation: mechanisms and management. Edited by Rodney H Falk and Philip J Podrid. (Pp 448; $119.) New York: Raven Press, 1991. ISBN 0-88167-831-7.

The strength of this contribution lies in the fact that the editors have invited and collected contributions rarely published together, so that we have in one modest volume a comprehensive account of the subject. Those looking for definitive answers may not find them, however. There are for example two separate chapters dealing with pathology, from slightly different aspects, where one single and authoritative chapter would have suited most readers.

Clinicians not already aware of the way in which the multiple wavelet theory has been refined and illustrated will find the chapter by Janse and Allessie illuminating. The various causes for atrial fibrillation, the way in which it can express itself under different circumstances, and the range of medications available as well as newer techniques for ablating the atrioventricular node all receive extensive discussion.

Among the chapters worthy of special consideration is that by Coumel on the neural aspect of paroxysmal fibrillation, a consideration not widely discussed in publications in English language journals; epitomised, perhaps, by the fact that the chapter preceding his, on idiopathic atrial fibrillation, does not cite his work. The final chapter, by the editors, is described as an overview of the management of atrial fibrillation but in essence it is a brief account of all aspects of the subject, in what seems to be an attempt to correlate aetiology with specific forms of treatment under various circumstances.

Whatever the authors had done they were bound to run into difficulties with regard to atrial flutter, which does not receive separate consideration or correlation except in passing.

If consulted with care and with knowledge of the approach adopted by the editors, there are many facets of atrial fibrillation covered here that will be of interest to all, and, with this proviso, this has potential value for a wide range of readers.

DENNIS M KRIKLER

The titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add £2 per item for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (MasterCard, VISA, or American Express) stating card number, expiry date, and your full name.

BRITISH CARDIAC SOCIETY NEWSLETTER

Annual Meeting at Harrogate

The Harrogate meeting was judged a success. Over 900 physicians and surgeons attended over the three days. In addition 350 cardiac nurses came to the part of the meeting arranged for them. There were 100 at the technicians programme. The 150 oral presentations were generally of a high standard, and the 120 posters were well received. Overall we were able to accept 39% of the abstracts that were submitted, but the figure could well have been higher if more time had been available. We were delighted to welcome Dr Eugene Braunwald for the Thomas Lewis Lecture, and Raphael Balcon's St Cyres Lecture was another highlight. John Parker arranged a very informative and somewhat worrying session on the internal market that was well attended though it had to be scheduled at the end of the sessions originally planned for the day. The presentations for the Young Investigators Award were of a high standard. The judges—who included Professor Lars Rydén from Gothenburg—awarded first prize to Hugh Watkins for his paper on the Clinical Application of Molecular Genetic Analysis in Familial Hypertrophic Cardiomyopathy, but found it impossible to separate the remaining three finalists. The position of runner up was therefore shared by Stematis Adamopoulos, Guy Haywood, and Nicholas Peters. The dedicated session for district hospital cardiologists proved a very popular innovation, and is likely to remain a feature in subsequent meetings. It would be unrealistic to expect that nothing could be criticised, however, and as always we have noted some areas that will require more attention next year. We will be glad to receive comments—especially constructive adverse ones.

We welcomed Professor Robert Slama as President of the French Cardiac Society and Professor Rudolf Juchems representing the German Cardiac Society.

We intend to maintain and develop such relationships that have been established in recent years—to a degree that we already enjoy with our Irish colleagues. Council has expressed a wish to invite representatives from additional European societies in future years, a development that accords well with the trend to increasing European cooperation.

Future Annual Meetings

Torquay, Glasgow, and then Harrogate . . . These successive venues for the British Cardiac Society annual meeting have convinced members that venturing outside London has considerable advantages. We see parts of the United Kingdom that many of us do not know well, and those of us who work in the south east can more easily resist the temptation to put in a little time at the hospital. Because we are more confined, we have more opportunities for formal and informal gatherings, and the meetings therefore feel more cohesive. We are committed to Wembley next year and to Torquay in 1994. But members at the recent annual general meeting decided by a unanimous show of hands that we forego the option of returning to Wembley in 1995 in favour of Harrogate. An additional factor that may have influenced opinion was the increased cost to the Society of meetings in London. We have to face much higher expenditure these days because of the expansion in the activities of the Society: a fall in income could force us to reduce our financial reserves that we are anxious to keep at a prudent level. These considerations do not preclude maintaining Wembley in a rotation of venues, and indeed many members from other parts of the country have expressed a wish that we do so. We would prefer to introduce more variety than a four-way rotation between Wembley, Glasgow, Torquay, and Harrogate but we are constrained by the size of the site we require for sessions plus exhibition. Other possibilities are Birmingham (which is expensive), Belfast, Edinburgh, and Bournemouth. No decisions have yet been taken for beyond 1996 when we will be in Glasgow again, but they must be made soon because of the pressure on bookings at the major conference centres. Our recent meeting had to coincide with half term—an unpopular piece of timing. We hope to avoid this in future, but we need good planning—plus inside reliable information from the education authorities.

Developments within the Society

Our premises in Fitzroy Square have five levels. The basement is now equipped as a seminar room that we hope will be well used. In addition to our own teach-ins and workshops as well as the requirements of the affiliated groups, the Officers would be prepared to consider applications from members who are seeking a venue for small cardiac meetings of up to 35 people. The criteria that would be applied in judging suitability would be based on the current philosophy of the society, and no doubt these can be codified as experience increases. The ground floor is used for a reception area and administration. When our resources permit more expenditure, this area will be decorated in a manner appropriate to a Georgian house: at present it is acceptable but uninspiring. On the first floor we have a board room and the principal office. The second floor houses the editorial offices of the *British Heart Journal*, and the joint offices for the affiliated groups—now in the process of moving in. On the third floor we have the new premises of the Resuscitation Council of the United Kingdom—an organisation that will be playing an increasing role in maintaining standards and providing instructor courses in basic and advanced cardiac life support. One large room remains unoccupied, but one of our sister societies is interested in the possibility of moving in, and negotiations are in progress.

We have already mentioned our need to increase the number of permanent staff in the house. Tribute should be paid to Elaine Brown and Jennie Lodge who have faced a huge expansion in the commitments of the Society. We have had an overwhelming response in our quest to fill the new post of Executive Secretary. The task of drawing up a short list has been formidable, but an appointment should be made on 2 July. Suitable staffing arrangements must also be agreed with the affiliated groups and for the Resuscitation Council. We will give more news next month.

Research and audit

We gave the hot news last month of final arrangements for funding the RITA 2 (Randomised Intervention for Treatment of Angina 2), trial with the principal contributions from the British Heart Foundation and the Medical Research Council. The Society had supported the feasibility and pilot studies. We now have more information on successful applications for two other projects that involve the British Cardiac Society; these are related to our audit activities. Funding is coming from the Department of Health through the research unit of the Royal College of Physicians that is directed by Dr Anthony Hopkins. (Our own committee is managed jointly with the Cardiology Committee of the College). The scrutiny of delays from the onset of symptoms to receipt of thrombolysis has been managed very successfully by John Birkhead. The results of the pilot study involving six hospitals will be published in the *British Medical Journal*, and the audit committee now intends to expand it to 25 centres. These may change from time to time depending on the total duration of the project. The purpose of the audit—mentioned in a recent newsletter—is to allow hospitals to make anonymous comparisons of their own performance in the utilisation of thrombolytic therapy with that of other centres. The pilot study showed that this can be a powerful stimulus to improvement. The observations are relatively simple and will have little impact on the work load of nurses and junior medical staff, but they add interest to routine work. Several hospitals have already applied to join the scheme. Application can be made directly to John Birkhead at the General Hospital, Billing Road, Northampton NN1 5BD. The second project that will be funded is the valuable Confidential Enquiry into Complications of Cardiac Catheterisation (CECCC), which has already expanded its activity under the direction of David de Bono.

Plants in Cardiology

How many members at Harrogate saw the elegant monograph based on the series in the *British Heart Journal* by Arthur Hollman on *Plants in Cardiology?* It was on the Journal stand as a new BMJ publication, but perhaps not prominently displayed because we at least missed it... There can be few members of the Society who would not wish to have a copy. The author is known to most of us, but it seems appropriate to reproduce part of what is written on the back cover. "Dr Hollman is a cardiologist who is also a keen amateur botanist, a Fellow of the Linnean Society, and a member of the Committee of Management of the Chelsea Physic Garden. He has woven medical and botanical information into succinct and elegantly written articles. Written primarily for cardiologist, his book will also be valued by everyone interested in nature's contribution to medicine, including doctors, pharmacists, botanist, herbalists, and medical historians. A glossary explains the most commonly occurring drug names and medical conditions for the non-technical reader. With its full page illustrations of plants reproduced from original sources such as Gerard's seventeenth century *Herball* and Bentley's and Trimen's nineteenth century *Medicinal Plants*, this is a beautiful record of cardiological discovery." Indeed it is. Copies (ISBN 0-7279-0744-1) can be obtained from the BMJ Publishing Group, BMA House, Tavistock Square, London WC1H 9JR, or from all medical bookshops including the BMJ bookshop at BMA House (071 383 6185). The price of £5.95 includes postage. Publication may not have gone ahead without modest support from the Society, but we are confident that the book will be popular and that our investment will be justly rewarded.

Cardiology in Europe

This is the first of regular news items concerning cardiology in Europe from Philip-Poole-Wilson. "Links, exchanges, and friendships have increased substantially over the last two decades between cardiologists in Europe and Britain. These interactions will become more common with the greater freedom of movement for doctors that will begin in 1993.

The rapid expansion of the European Society of Cardiology began in the 1970s but accelerated when the Congresses became an annual event after the Vienna meeting of 1988. Previously they had been held every four years. The European Society is made up of the National Societies of 32 countries that stretch from the Atlantic to the Urals, and from Northern Norway to the Mediterranean. All members of national societies are members of the European Society through their links with a Working Group. The British Cardiac Society is well represented within the Working Groups and other committees of the European Society of Cardiology.

This year the annual congress takes place in Barcelona from 30 August to 3 September. Almost 7000 abstracts were received, an increase of 25% on the figure for 1991. In future, attempts will be made to increase the acceptance rate to more than 30%. The United Kingdom was third, behind Germany and Italy, in the number of abstracts submitted; second, behind Germany, in the number accepted; and first in the proportion that were accepted. This gratifying position is not one that we have always achieved in past years.

The dates and venues of future congresses of the European Society of Cardiology are: 1993 Nice, 29 August to 2 September; 1994 Berlin, 10 to 14 September (a World congress, in conjunction with the International Society and Federation of Cardiology (ISFC)); 1995 Amsterdam, 20 to 24 August; 1996 Birmingham, 25 to 29 August; 1997 Stockholm, 24 to 28 August.

The closing date for abstracts is always 14 February except for 1994 when the closing date will be 1 December 1993. Attempts are being made to avoid the last two weeks of August. But the congress is now so large that the availability of venues for the congress has become a major problem. The goal is for the congress to take place during the first half of September, but this will not be achieved for several years."

News of colleagues

New appointments to consultant posts include Oliver Ormerod at the John Radcliffe Hospital, Christopher Travill at the Luton and Dunstable, and Adeniyi Molajo at Leigh Hospital in Wigan. We have heard with regret of the death on 4 April of Professor Albrecht Fleckenstein.

Reminders for diaries

The first in the series of the Society's Workshops will be on Preventive Cardiology on 14 October, organised by David Wood, and the teach-in on "Emerging Concepts in Atherogenesis" on 10 November is being arranged by Michael Davies. These will both be at Fitzroy Square. Finally, the British Cardiac Society and the Resuscitation Council of the United Kingdom (now more closely associated with us at 9 Fitzroy Square) both have an interest in "Resuscitation 92" in Brighton Conference Centre on 20 and 21 November. Application for all three can be made to the Society.

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NOTICE

The 1993 Annual Meeting of the **British Cardiac Society** will take place at the Wembley Conference Centre from 18 to 21 May.

CIA software—well written and "user-friendly"

Confidence Interval Analysis (CIA) is a computer program that takes the sweat out of calculating confidence intervals. Devised by Martin Gardner, professor of medical statistics, MRC Environmental Epidemiology Unit, University of Southampton. The program is menu driven with easy access to each chapter and to the method required within each chapter. Topics covered include calculating confidence intervals for:

- means and their differences
- proportions and their differences
- regression and correlation
- relative risks and odds ratios
- survival analyses
- non-parametric analyses

For each method relevant intermediate statistics and the required confidence interval are produced on the screen. Complete with its own manual, the program may also be used in conjunction with the book *Statistics with Confidence* (see below), which provides numerous worked examples. The software is available for IBM compatibles on either a 5¼" or a 3½" disk.

> ". . . well written, "user-friendly" . . . an invaluable companion to the book and recommended highly."
> *British Journal of Anaesthesia*

> ". . . highly recommended to doctors (and statisticians). *CIA* . . . will save a lot of time and pain."
> *British Medical Journal*

> ". . . an efficient and precisely focused piece of software."
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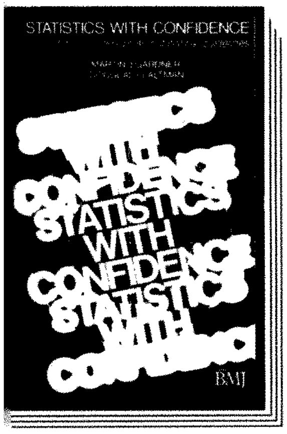

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Congestive heart failure: Adults (including elderly): initially 2.5mg daily in hospital under close medical supervision, increasing to 5-20mg once-daily according to response. Monitor blood pressure and renal function.

Renal impairment: May require lower maintanance dosage.

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PRECAUTIONS: Assessment of renal function is recommended. Symptomatic hypotension may occur, particularly in volume depleted patients and congestive heart failure. Caution in patients with ischaemic heart or cerebrovascular disease; renal insufficiency; renovascular hypertension. Patients with a history of angioedema may be at increased risk of angioedema with an ACE inhibitor. Cough has been reported with ACE inhibitors. Renal impairment (usually reversible) may occur in some patients. Hypotension may occur during surgery or anaesthesia. Caution in nursing mothers. No paediatric experience. Afro-Caribbean patients may show reduced therapeutic response. Symptomatic hypotension can be minimised by discontinuing diuretic prior to 'Zestril'. Interaction with indomethacin and lithium. Potassium supplements, potassium sparing diuretics and potassium containing salt substitutes not recommended.

SIDE EFFECTS: Hypotension, dizziness, headache, diarrhoea, cough, nausea, fatigue. Less frequently, rash, asthenia. Rarely, angioneurotic oedema and other hypersensitivity reactions, myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients, palpitation, tachycardia, abdominal pain, dry mouth, hepatitis, jaundice, mood alterations, mental confusion, urticaria, diaphoresis, uraemia, oliguria/anuria, renal dysfunction, acute renal failure, impotence. A symptom complex which may include fever, vasculitis, myalgia, arthralgia/arthritis, positive ANA, elevated ESR, eosinophilia, leukocytosis; rash, photosensitivity or other dermatological manifestations may occur. Increases (usually reversible) in blood urea, serum creatinine, liver enzymes and serum bilirubin. Decreases in haemoglobin and haematocrit have occurred. Hyperkalaemia.

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'Zestril' is a trademark.

Further information is available from: ICI Pharmaceuticals, King's Court, Water Lane, Wilmslow, Cheshire SK9 5AZ.

REFERENCES: 1. White WB, Dey HM and Schulman P. Am Heart J 1989; **118:** 782-795. **2.** Kannel WB. Am J Med 1983; **75:** 4-11.

c/Nc/

OCTOBER 1992 VOL 68 No 4

BRITISH HEART JOURNAL

NCM

In association with the British Cardiac Society

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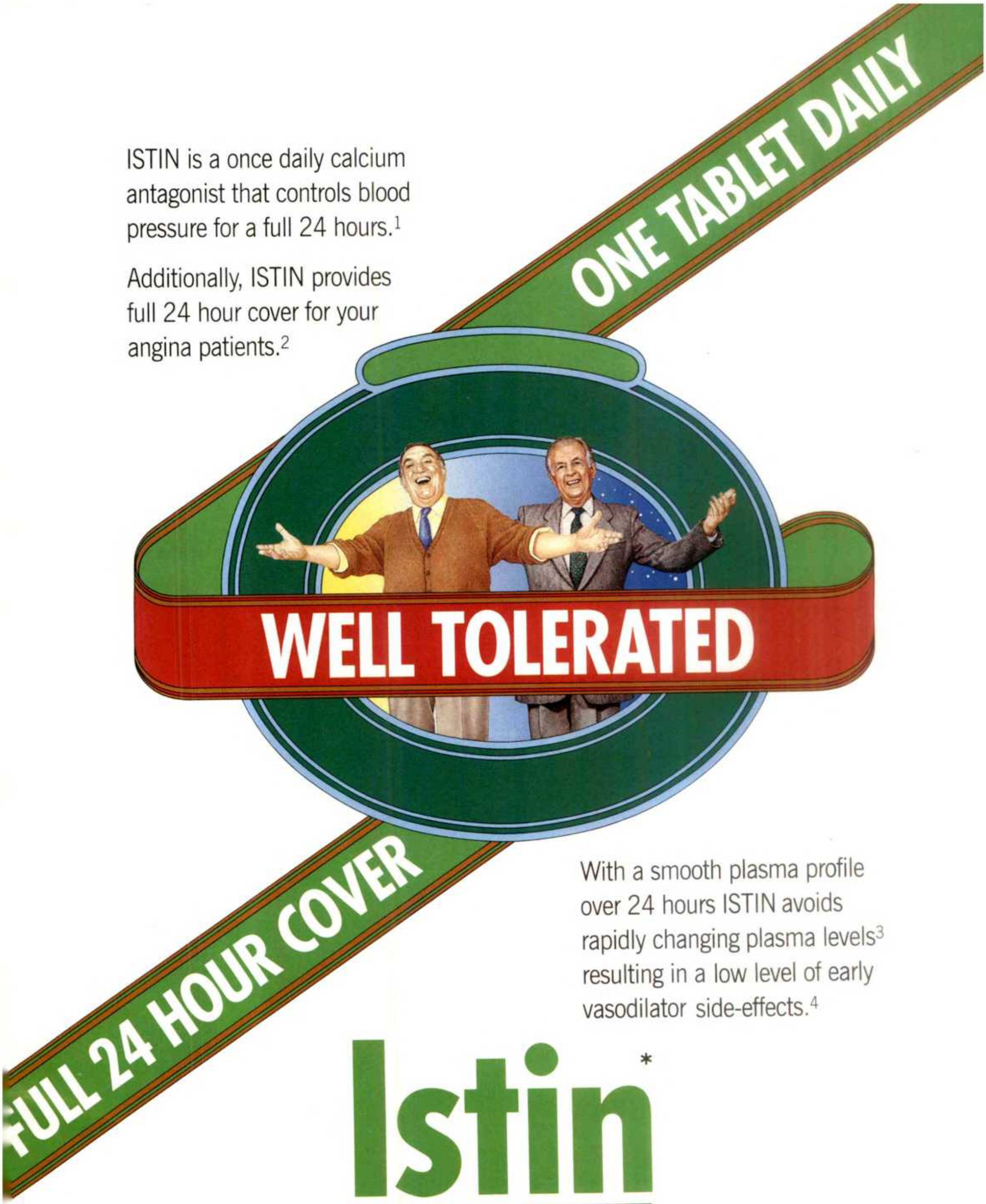

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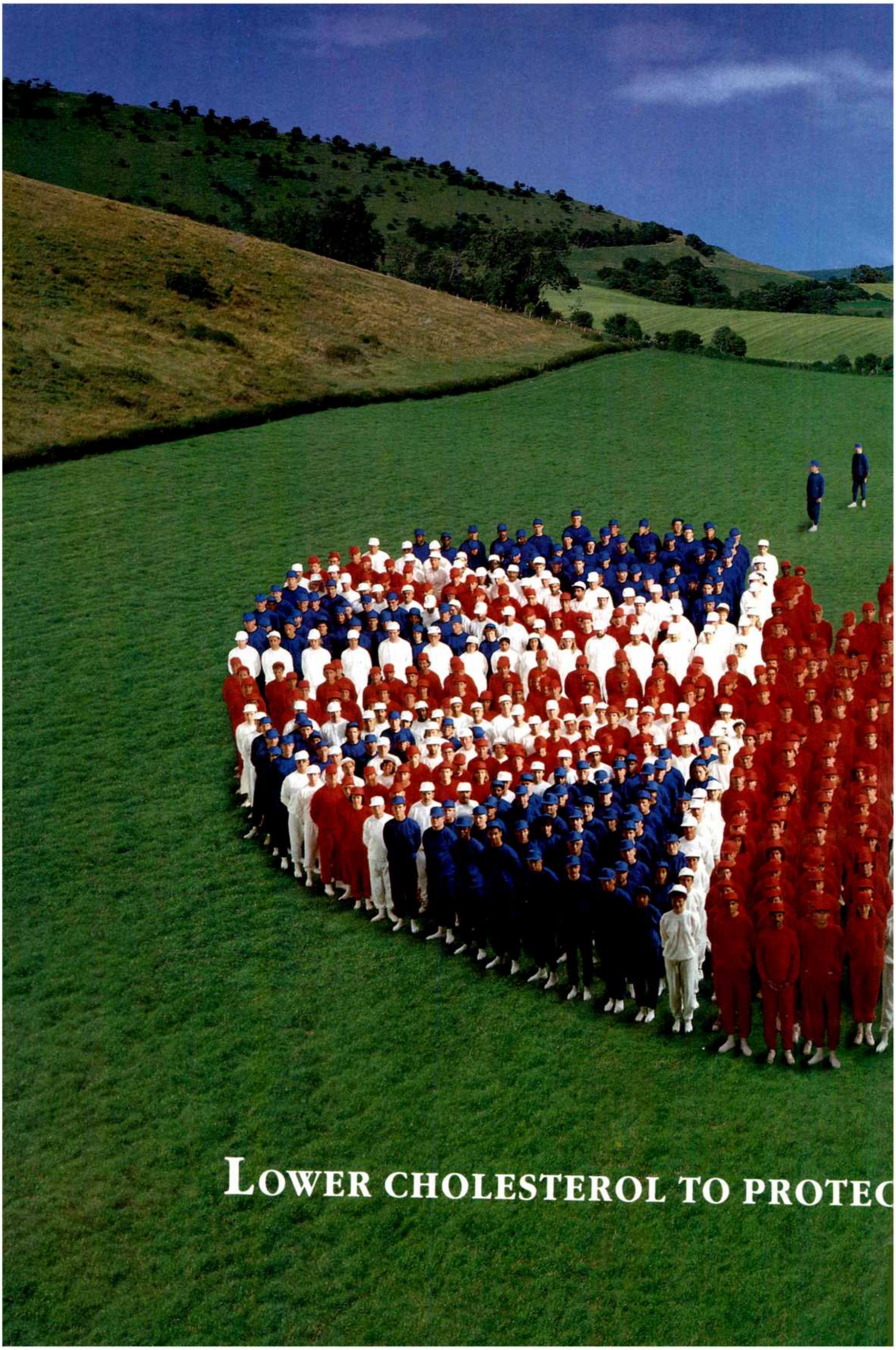
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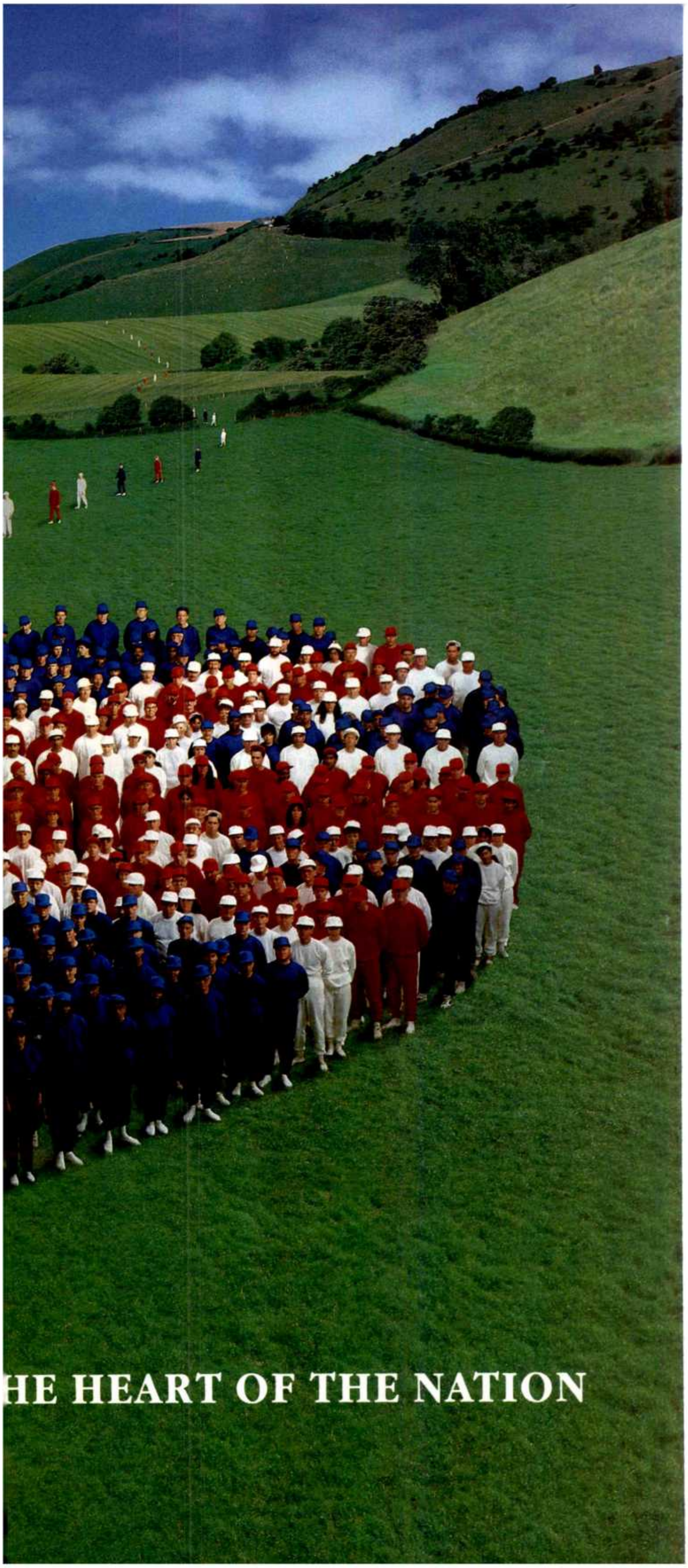

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BASIC NHS COST 10 mg tablets, £18.29 for 28-tablet calendar pack. 20 mg tablets, £31.09 for 28-tablet calendar pack.

Product licence numbers: 10 mg tablets, 0025/0241.
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REFERENCES
1. OPCS Monitor DH2, June 1990.
2. Lipid Research Clinics Program. *J. Amer. med. Ass.*, 1984, **251**, 351.

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References: **1.** Chung M *et al. Hosp Formul* 1990; **25** (Suppl A): 15-19. **2.** Cruickshank J M & McCainsh J. *Acta Therapeutica* 1992; **18:** 53-59. **3.** Data on file.

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Br Heart J 1992;68:345

BRITISH
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Editorial

Speeding up the review process

Over the past ten years the *British Heart Journal* has been a financial and scientific success. Changes in scientific publishing dictate that the Journal must change to maintain this position. A computerised tracking system for manuscripts and reviewers has now given us the opportunity to streamline the decision making process. This change will be welcomed by our contributors, some of whom perceive that the time taken between submission and final acceptance is too long.

The interval between submission and decision on an article has many components. A major factor is the time taken by reviewers to return reports. We all endorse peer review as the foundation of scientific publishing. Yet there is a price to pay, that of delay. The number of scientific articles written world-wide continues to rise, as does the use of reviewers' time. A review takes time and effort: a detailed review of a difficult article takes us at least an hour. Published data on reviewers activities suggest that many take longer.[1 2] Why do reviewers review? The most frequently used argument is that reviewers being members of the scientific community have an academic duty to do this work. To the busy clinician this is not always a compelling argument. Some journals seek permission from the reviewer before sending an article: we do not have the office capacity to do this. Some reputable journals pay reviewers a modest sum, but this would be an unacceptable financial drain on the *British Heart Journal.*

In consultation with the Editorial Committee of the *British Heart Journal* we have decided on changes that will speed up the review process. Six additional United Kingdom members are being added to the committee, and representatives from mainland Europe and the United States of America are being proposed. The number of reviewers is to be increased. We are keen to capitalise on the specialist knowledge of lecturers, senior research fellows, and senior registrars within their own areas of interest.

The way in which submitted manuscripts are handled is to change. As before, the corresponding author will receive a postcard giving the date on which the article was received and a code number. But in future the paper will be sent to external reviewers and to at least one member of the editorial committee. Authors may suggest three suitable external reviewers. While we will normally use one or more of the suggested names we reserve the right not to do so.

The editorial committee members will comment rapidly on how appropriate the article is for the *British Heart Journal* and indicate the degree of importance while noting any obvious flaws. External reviewers will continue to make more detailed criticisms. The reports will be considered jointly by the editor and associate editors, and, where appropriate, one of the assistant editors and a statistical expert. We will meet regularly and will decide on the status of each article within twelve weeks of the submission date. We will be able to tell most authors the decision well within this time. If they wish, authors with fax machines can receive the answer even more quickly. The decision will be—accept, reject, or accept subject to *specific* revision by the authors within one month.

Articles will be revised less than in the past. In a sense the *British Heart Journal* by accepting an article gives it a stamp of approval, but if authors are pressed by the Journal to answer all the reviewers' criticisms they may end up writing an article that does not say what they originally intended. Fewer revisions may lead to a vigorous correspondence column pointing out different interpretations of a paper, and this is what we would like to encourage.

Any decision process should have an appeal mechanism. The selected reviewers may have been ill-informed on a particular topic. Our rejection letter will indicate whether the decision was based solely on reviewers' criticisms, or on broader issues of interest or suitability. Authors can resubmit, pointing out why they consider the review is unfair. A new set of reviewers will be used to assess such submissions.

The new system of handling submissions will depend heavily on the efforts of the office staff, the editors, and members of the Editorial Committee to maintain its momentum.

M J DAVIES
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1 Lock S, Smith J. What do peer reviewers do? *JAMA* 1990;263:1341–3.
2 Yankauer A. Who are the peer reviewers and how much do they review? *JAMA* 1990;263:1338–40.

Br Heart J 1992;68:346–7

Editorial

How can myocarditis be diagnosed and should it be treated?

Myocarditis remains an enigma. On one hand it is a diagnosis which is suspected clinically when sudden cardiac failure or arrhythmias or both follow a febrile 'flu-like illness. On the other hand, myocarditis has a defined histological appearance with evidence of myocyte damage and a lymphocytic interstitial inflammatory infiltrate. The similarity between this histological picture and acute rejection led naturally to the suggestion that immunosuppression might be a useful treatment.[1] Regrettably the clinical and pathological facets of the disease often do not coincide, and the reported frequency of a biopsy positive confirmation of the clinical diagnosis has at best been variable. Leaving this difficulty aside it was unclear whether any form of treatment influenced the ultimate outcome.

Clinical experience showed that in the short-term some patients recovered spontaneously, others died. Longer term follow up showed that some patients had impaired left ventricular function and some late deaths occurred. Individual clinicians did not see enough cases to assess the impact of steroid or immunosuppressive treatment.

A large trial was initiated by Jay Mason at the University of Utah Medical Center to answer specifically the question of whether immunosuppression improved prognosis. A panel of international experts in the histology of myocarditis met in Dallas, and laid down strict criteria for the diagnosis and terminology used in reporting on the biopsy specimens.[2] The preliminary results of the trial were reported to the American College of Cardiology meeting in Dallas in April 1992 and were discussed in the ACCEL (American College of Cardiology Extended Learning) programme for May 1992.

As its starting point the trial recruited patients with a short history (<2 years) of unexplained congestive heart failure. All underwent cardiac biopsy, and a patient could only enter the trial if a biopsy specimen showed acute myocarditis and the ejection fraction was less than 45%. The first point of major interest was that in over 2000 subjects fitting the clinical criteria the local pathologist reported myocarditis by histological criteria in only about 200. Only 111 of these were available for randomisation: the others were excluded because they had good left ventricular function or because they refused to take part in the trial. Patients who consented to the trial were randomised to treatment with cyclosporin and prednisone with heart failure treatment over 24 weeks or to treatment for heart failure alone. A third arm to the trial using azathioprine was stopped at 14 months owing to the low patient recruitment rate and the need to reduce sample size requirements. Sixty four patients were treated with immunosuppression and 47 controls were given conventional treatment for heart failure. Many patients in both groups showed an improvement in left ventricular function but this was not significantly different in those treated with immunosuppression and those who were not. Death rates at one and two years were not significantly different. A further interesting aspect of the trial was that when all the biopsy specimens were reviewed by the Dallas panel of pathologists only about two thirds were confirmed as showing histological acute myocarditis. The most significant clinical improvement occurred in those with histologically confirmed myocarditis, whether or not they had been treated with immunosuppression.

The trial showed that histologically confirmed acute myocarditis is rare. Previous pathological studies that suggested that the disease was more common may either have coincided fortuitously with an outbreak of a particularly cardiotoxic virus infection in the community or have used less rigorous diagnostic criteria than the Dallas panel. A major difficulty in histological interpretation is the identification of the nature of small round dark cells in the interstitial tissues. Only if these cells can be identified as lymphocytes by immunohistochemistry is the diagnosis of myocarditis justified. In future the standard minimum criterion for acute myocarditis should be an infiltrate of interstitial cells that are shown to be T lymphocytes by immunohistochemical marking.

The second message of the trial is that many patients recover with a considerable improvement of left ventricular function. Treatment with cyclosporin and steroids is neither harmful nor beneficial.

The study does raise interesting and unanswered questions that the fuller reports of the trial may in part answer. If most patients did not have histological myocarditis, what was suppressing left ventricular function? It may be that the histological appearances used to diagnose myocarditis are too rigorous. Could a virus infection suppress myocardial function without inducing myocyte necrosis and inflammation? The use of in situ hybridisation to demonstrate viral genomes, when probes are available for all the viruses known to be cardiotoxic, may answer this point. Could humoral antibody mediated damage rather than cellular immunity be present, with the short-term deposition of immune complexes in the myocardial microvasculature? The more detailed report of the myocarditis trial may show whether immune activation in the myocardium indicates subgroups that are either at higher risk or would respond to immunosuppression.

Many of the subjects without histological myocarditis did have abnormal biopsy specimens showing myocyte hypertrophy and interstitial fibrosis. These features suggest a process that is more longstanding than indicated by the clinical history. Thus it seems that some subjects in whom a dilated cardiomyopathy is already established remain well for long periods before sudden undergoing decompensation. It may be that the acute myocarditic phase is short, and that in many patients this phase was over before a biopsy specimen was taken.

What do these findings mean in practice in a patient with a clinical diagnosis of acute myocarditis? Diagnostic biopsy, if it is undertaken solely to establish myocarditis by routine histological methods with a view to starting immunosuppression, is now not justified—because the findings will not influence treatment.

The trial should not be used to discredit the overall practice of performing cardiac biopsies. Biopsy specimens are useful in many conditions and are essential to the management of cardiac transplantation. Biopsies are an integral part of investigating restrictive cardiomyopathies and the only way to confirm cardiac amyloid.[3] The amount of fibrous tissue in the myocardium can give some prognostic information in cardiomyopathies. The aquisition of myocardial tissue for immunological and virological studies is vital if the pathogenesis of human myocarditis is to be unravelled. Biopsy specimens should continue to be taken as part of a formal research protocol: the value of the Mason trial may lie in what is learnt about the mechanisms of immunological damage to the myocardium. What is no longer necessary, and indeed hard to justify, is occasional cardiac biopsy for the sole purpose of making a tissue diagnosis of myocarditis.

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VIEWPOINT

Answers to complex questions cannot be derived from "simple" trials

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As we progress in the exciting area of treatment of acute myocardial infarction, two clinical trial methodologies coming from different philosophies and traditions must be considered. Smaller (200–3000 patient), detailed trials focusing on pathophysiology will be referred to as "mini-trials", while mammoth studies (10 000–50 000 patients) designed to measure mortality rates will be referred to as "mega-trials." In the field of coronary thrombolysis, examples of mini-trials include the continuing efforts of the Thrombolysis in Myocardial Infarction (TIMI) Group, the European Cooperative Study Group (ECSG), and the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Group.[1-8] The major mega-trials have been conducted by the Gruppo Italiano Per Lo Studio Della Streptochinasi Nell' Infarcto Miocardico (GISSI) and the International Studies of Infarct Survival (ISIS) Groups.[9-11] Both types of trials have proved to be essential to our understanding of thrombolytic intervention, and in most ways the two designs are quite complementary. In this paper, in contrasting the two designs, we will highlight the critical contribution of the mini-trials and then provide insight into the opportunity provided in an ongoing mega-trial to investigate the differences in the approaches (table).

General philosophy: mini-trials

Individual mini-trials are designed to provide a small piece in the overall puzzle of the mechanisms by which disease states operate and the mechanisms by which interventions affect the disease process. These trials are particularly suited to the evaluation of new mechanical or pharmacological strategies while they are in evolution. The mini-trial strategy carefully measures the *intended* target of the treatment in patients receiving the intervention and in patients not receiving the intervention. The data are required with maximum precision by a pre-specified protocol and an effort is made to control all other confounding factors (ancillary therapy) except for the therapy being randomised. Entry criteria are restricted to the group of patients expected to benefit most by the purported mechanism of action of the intervention. Biological markers, such as coronary perfusion, left ventricular function or haemostatic indices are measured whenever possible. More global clinical outcomes are measured (mortality, cost, quality of life) to provide a context in which to judge the likely overall effect of the treatment. The individual data items are usually monitored by individuals independent of the clinical site to ensure that all data are accurate.

The mini-trial allows for a special exchange of ideas among a focused group of investigators. Protocols can be developed through round table discussions and frequent site visits can be made to improve the spirit of collaboration and common purpose. The data generated can be reviewed by all investigators, each of whom can have input into published papers and can achieve academic recognition. All of these characteristics foster a highly interactive and enjoyable working relationship among the investigators and research coordinators.

Problems have arisen with the interpretation of mini-trials when they have been used

Summary of major features that distinguish two classes of clinical trials

Mega-trial	*Mini-trial*
Large population (> 10 000)	Small population (< 3000)
Large number of clinical sites (200–2000)	Limited number of sites (4–30)
Minimal data collected/patient	Maximal data collected/patient
Protocol algorithm simple	Algorithm more complex
Entry criteria wide	Entry criteria more restricted
Cannot control ancillary care, treatment	Complete protocolisation of care possible
Data not quality assured	Full quality assurance of data
Cannot assess advanced technology or avant-garde or high risk therapy	Can assess *any* technology or therapy
Cannot probe the mechanism of therapy (reductionist)	Mechanistic focus
Limited knowledge of safety data during study's progress (lag)	"On-line" assessment of safety parameters
Key end point is mortality reduction	Focus on many non-fatal, important outcomes (for example, stroke, reinfarction, revascularisation, cardiac function, economic, quality of life)
Have not been used to establish drug dosing	Excellent means of establishing drug dosing
Long obligatory time lag of initiation	Can be started expeditiously

to draw conclusions which their design could not support. First, the critical educational effort of the ISIS group has been instrumental in bringing the importance of sample size into the clinical consciousness.[12] Medical treatments that reduce mortality by more than 25% are rare, so that sample sizes of more than 8000 patients are needed for most trials in acute myocardial infarction in order reliably to detect treatment effects. Finding "no difference" in mortality in an individual mini-trial is not adequate evidence by itself that a treatment should be abandoned. Secondly, mini-trials are designed to evaluate the impact of therapy on *intended* targets of the intervention based on current understanding of pathophysiology. Published reports include many examples of how rapidly our understanding of pathophysiology can change as large enough trials are completed to measure the effect of therapy on the *unintended* target. Classic examples of this problem include the finding that suppression of arrhythmias could be achieved with certain "anti-arrhythmic" agents, but the rate of sudden death actually increased (Cardiac Arrhythmia Suppression Trial (CAST)) and the finding that although calcium channel blockers can improve diastolic dysfunction or prevent coronary vasospasm, mortality in patients with reduced left ventricular function is increased by these agents. Finally, the almost irresistible urge to evaluate small subgroups in mini-trials can lead to erroneous conclusions because of the play of chance. The exclusion of elderly patients and patients with inferior infarction from thrombolysis because of subgroup analysis provides an excellent example of the difficulty with this approach. The ISIS investigators have emphasised the fact that "quantitative" differences are common, but that qualitative differences are uncommon. Treatments that have a positive effect in a disease state rarely have detrimental effects in particular subgroups, but differences in the magnitude of treatment effects are common.

Angioplasty after thrombolysis

In 1985 before the landmark GISSI-1[9] trial had been completed we launched the first multicentre TAMI trial in which we assumed that thrombolysis would be the mainstay of treatment, but that the roles of coronary revascularisation and adjunctive therapy would become the major foci of investigation. Indeed several trials investigated mechanical revascularisation including TAMI,[1-4] TIMI,[5 6] the ECSG trial,[7 8] and Should We Intervene Following Thrombolysis? (SWIFT).[13] Collectively, these mini-trials indicated that routine coronary angioplasty is not necessary after thrombolysis on either an emergency or elective basis.[1 5 6 8] These studies had a major impact on avoiding unnecessary angioplasty in the United States[14] and helped to focus biomedical research on better methods of stabilising the unstable atherosclerotic plaque with antiplatelet and antithrombotic therapy.[14]

Because these trials evaluated an expensive, evolving technology the requirement for universal availability of coronary angioplasty and angiography facilities would have prohibited the mega-trial networks from performing the trials. The documentation of coronary patency, detailed data collection, standardised ancillary medical treatment, and post-discharge functional evaluations provide a rich source of data to guide practice in various areas of importance to these patients.[1-8 13 14] In particular, the detailed information about complications has led to new insight on risk factors for intracranial bleeding and the impact of reocclusion of the infarct-related artery.

General philosophy: mega-trials

The mega-trial philosophy rests on the general principles described above and the belief that large numbers of patients will obviate the need for detailed data collection, measurement of pathophysiologic end points, and specification of ancillary therapy. In fact, detailed and restrictive protocols are seen as impediments to the primary goal: large numbers of *randomised* patients. The sheer volume of data is expected to "average" out the random error effects of imprecise data collection and confounding treatment effects. The success and impact of the mega-trial concept are self-evident.

Overextending the bounds allowed by mega-trial methods, however, also leads to considerable problems. The mega-trial philosophy is by definition reductionist; the treatments administered must be universally available and the method of administration must be feasible in all centres. Thus the mega-trial alone cannot be taken as definitive documentation of the relative efficacy of a class of treatment, because different dosing and monitoring strategies can have a profound effect on biological and clinical outcomes. Voluminous data are now available to demonstrate that "high-tech" environments lead to low mortality in certain conditions, presumably because of the increased ability to regulate therapy based on informed monitoring. This issue has come to the forefront with regard to heparin co-administration with thrombolytic therapy.

The mega-trial methodology of simple data forms and no interference with clinical practice prevents direct investigation of pathophysiological mechanisms. In the ISIS-2 trial oral aspirin led to nearly the same mortality reduction as intravenous streptokinase (odds ratio 0·21 and 0·26, respectively).[11] However, the mechanism for this observation was left unexplained. Although the reported reinfarction rate in ISIS-2 was reduced nearly 50% from 4·2% to 2·4%, the low absolute event rates preclude this reduction in reinfarction rates from accounting for the striking reduction in mortality, especially since most reinfarction events did not lead to death. Was the mortality reduction afforded by aspirin due to more rapid coronary thrombolysis, less re-thrombosis, or an anti-inflammatory effect on the myocardium or infarct vessel wall? Such complex mechanistic issues, which must be understood if more effective therapy is to be developed, could only be explored by a mini-trial in which all factors were systemically examined.

Just as the value of the mini-trial can be overextended, the mega-trial concept can lead to speculative assertions not supported by the methods. In general, end points other than mortality are probably under-reported in mega-trials because the data are not verified. This particularly becomes a problem when patients are transferred from one hospital to another and no mechanism is in place for continued data collection. Furthermore, the lack of precise definitions and absence of standardised methods of data collection (for example, collection protocols to detect reinfarction) preclude a confident estimate of the true rate of complications related to a treatment, although comparisons of relative event rates between treatments remain feasible. This issue becomes particularly important when differences in mortality are small, but outcomes affecting critical areas of quality of life, such as stroke, may occur with different frequency in different treatment groups. Estimated incidence rates from mega-trials must be regarded with scepticism when composite estimates of the overall effect of a treatment are constructed.

Interchange of trial designs

A mega-trial can be initiated only after mini-trials have laid the groundwork. If early trials had not proved that thrombolytic agents effectively achieved myocardial perfusion and improved left ventricular ejection fraction, mega-trials might not have been undertaken. Another example of the interchange is the question of whether to treat patients with thrombolytic agents beyond six hours from symptom onset. Subgroup analyses from large scale trials generally show a favourable risk to benefit ratio,[11 15] but multiple subgroup analyses are fraught with potential incorrect conclusions, and the large GISSI-1 trial found no evidence of benefit in patients treated late.[9] Recently, a mechanistic placebo-controlled trial of tissue plasminogen activator showed that coronary thrombolysis can be achieved in these patients and that end diastolic left ventricular cavity size is preserved.[4 5] Other observational studies suggest that malignant ventricular arrhythmias can be suppressed by delayed infarct vessel recanalisation. Although these data are encouraging, a meta-analysis by Honan and colleagues raised the concern that delayed thrombolytic intervention may be associated with an increased risk of cardiac rupture.[16] The only method to determine where the balance lies between these mechanistic benefits and detrimental effects is through the completion of dedicated mega-trials such as the Estudio Multicentrio Estreptiochinasi Republico Americao Sud (EMERAS) and Late Assessment of Thrombolytic Efficacy (LATE) trials. The independent relation of the mini and mega trials is evident in the investigation of this issue, with each component providing independent, pivotal information.

Global utilisation of streptokinase and tissue plasminogen activator in occluded coronary arteries (GUSTO)

After conducting pathophysiologically oriented mini-trials for several years, in collaboration with investigators from 14 countries we are in the midst of a trial in which we intend to enroll over 40 000 patients. The main objective is to determine whether achieving early reperfusion (speed) and preventing reocclusion (permanence) leads to improved clinical outcomes. In this new mega-trial we have tried to hybridise elements of quality control and pathophysiological investigation from the mini-trials and the protocol simplicity of the mega-trials. We hope that this approach will lead to a more accurate data set that will allow the primary question to be answered while providing a source for investigation of the most appropriate methods for future large trials.

Although the data forms have remained brief (three pages) by mini-trial standards, enough details are collected to evaluate differences in baseline characteristics and incidences of morbid events. Questions are formatted so that the presence or absence of the outcome must be specifically noted. Training meetings are being held to emphasise the specific definitions agreed by the steering committee. Of course, decisions about which data items to place on the form were made much easier by the pioneering work of the GISSI and ISIS investigators.

Many more data are being collected in several key ancillary studies that were identified by the steering committee before the start of the trial. A 2400 patient angiographic study is being conducted as part of the trial, providing GUSTO with the ability to correlate the perfusion status in the angiographic sub-study with the clinical outcomes in the much larger population. Because of the intense interest in these areas, special information is being collected on all patients with stroke, reinfarction, and cardiogenic shock. A large, randomly selected population is being followed to allow a better understanding of quality of life, including resource consumption. By integrating these data from representative samples of the population, we hope to provide the foundation upon which the pathophysiological basis and societal implications of the mortality results can rest.

An independent organisation has been employed to audit 10% of the case records on a random basis with stratification so that each hospital is audited at least once during the trial. This system will allow us to verify the accuracy of the data from a mega-trial and provide a basis for estimating the degree of auditing that would be desirable in future mega-trials. The current mini-trial standard of 100% audit of case records may be a waste of time and money. A system for reporting major adverse events via facsimile has been developed to allow careful tracking of the progress of the study at the coordinating centre.

The combination of "softer" end point data and mortality results will allow us to validate composite clinical end points.[17 18] As our investment in biotechnology matures, trials will be needed to examine refinements in treatment, which will involve more fine tuning than merely comparing intervention with placebo. Since a mega-trial cannot be used to investigate every issue and in many cases, differences in mortality could not be expected, such factors as cost, return to work, prevention of hospital readmission, and freedom from non-fatal, adverse clinical events will become more important. Soft endpoints have been difficult to accept without evidence that they are also directly related to mortality.

Conclusion

Both types of trials are needed to advance the clinical treatment of acute myocardial infarction. Mega-trials can provide definitive evidence about the mortality reduction afforded by a class of therapy so that broad changes in clinical practice can be justified. Mini-trials can explain why a treatment is effective to allow development of more effective approaches attacking the identified mechanisms. Furthermore, the rationale for mega-trials and the "fine-tuning" of minor adjustments in treatment will be the task of the mini-trials. If reasonable composite clinical end points can be validated within the context of a large, simple trial and accepted by regulatory authorities and clinicians in the future, it is hoped that issues requiring mega-trial populations can be focused to maximise the amount of useful clinical information generated.

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VIEWPOINT

Beyond the mega-trial: certainty and uncertainty

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In the accompanying viewpoint (page 348) Topol and Califf describe and justify one of the largest clinical trials so far attempted; in GUSTO (Global Utilisation of Streptokinase and Tissue plasminogen activator (alteplase) for Occluded coronary arteries) some 40 000 patients will be recruited to compare the effects of streptokinase (SK), alteplase (rt-PA), and their combination with two different heparin regimes. Although opinions may vary as to the likely outcome of GUSTO, many will agree with the song from *Oklahoma*, that "things have gone as far as they can go": it is hard to envisage any rationale that would lead to a further order-of-magnitude increase in trial size. Furthermore, as trials of this size are so expensive and consume so much research activity in so many centres, there must be a practical limit to the number of very big trials that can be mounted at any one time in any particular therapeutic area. GUSTO will undoubtedly provide an answer to its primary objective and be the source of much additional information; but mega-trials are not a panacea for the limitations inherent in smaller studies.

Background

The randomised controlled clinical trial, double blind when feasible, is perhaps the most powerful tool that has been developed for the furtherance of patient treatment. Though little medical treatment is actually based on trial results, it is generally agreed that this should be the aim. In most instances (though with some notable exceptions) a new treatment is not introduced unless adequate trials have been performed. For 30 years cardiovascular developments have been based on state of the art clinical trials, and trial design and conduct have improved considerably as experience has been gained. The reason for the multiplicity of cardiovascular trials is in part clinical and part commercial: coronary artery disease is common and myocardial infarction is one of the main causes of acute medical admission to hospital, so not only is there a great need for improved treatments but also patients are readily available for inclusion in trials. Furthermore the pharmaceutical industry has no problem in providing finance because the market for its products is large. The increasing use of anticoagulants, β blockers, aspirin, and thrombolytics reflects both the progress of cardiovascular therapeutics and the maturation of trial design.

Past trials

ANTICOAGULANTS

The trials of indirect anticoagulants, phenindione, and warfarin, in the 1960s[1 2] were based on the misconception that clotting and thrombosis were the same thing. The trials were small—not even mini-trials according to Topol and Califf's definition. The Medical Research Council trials of 1964 and 1969 contained 383 and 1427 patients. The general principle that a larger sample size will increase the likelihood that a trial will confirm the existence of a small treatment difference is now widely accepted, but the need to examine this relation quantitatively and use this to determine trial size was not at that time understood (at least by clinicans) and by today's standards the results of these trials could never be regarded as more than suggestive. Nevertheless, it was believed that anticoagulants prolonged long-term survival after myocardial infarction, particularly in younger men with repeated infarcts. The anticoagulant story might have been followed up and resolved had the attention of cardiologists not been diverted by a sudden interest in arrhythmias.

BETA BLOCKERS

Because it was believed that suppressing arrhythmias would improve survival in myocardial infarction, and because β blockers had antiarrhythmic properties, a long series of small trials[3] followed the observation by Snow that propranolol did indeed improve survival.[4] These early small trials gave results that were at times conflicting and often confusing, and it was only when a trial of reasonable size (1884 patients, but still a mini-trial) was conducted with timolol[5] that an answer was obtained on which clinicians were prepared to base their practice. This was followed by similarly sized trials, not all of which gave equally convincing results (Beta Blocker Heart Attack Trial (BHAT) 3837 patients, metoprolol trial 1395 patients[6 7]) but nevertheless the place for β blockers after myocardial infarction was established. The place of antiarrhythmic therapy as such is still far from established, with a deleterious effect of antiarrhythmic agents having been demonstrated in the Cardiac Arrhythmia Suppression Trial (CAST).[8]

ASPIRIN

Trials of aspirin followed the same general pattern as those of β blockers: the early trials were small (1239 in the Welsh Study,[9] 4524 in the Aspirin Myocardial Infarction Study

(AMIS),[10] 2026 in the Persantine Aspirin Reinfarction Study (PARIS)[11]) and gave conflicting results and it was only with the publication of ISIS-2 (Second International Study of Infarct Survival) in which trial 17 187 patients had been allocated to treatment with aspirin or placebo that aspirin became accepted therapy.[12]

THROMBOLYSIS

With the experience gained in the anticoagulant, β blocker, and aspirin trials the way was open for a rapid advance when interest switched to thrombolysis. Here was an "old" treatment not adequately investigated,[13] and again the first of modern trials was inconclusive.[14] Then trials came along which were big in their day and the value of thrombolysis was proven. GISSI-I[15] (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico) included 11 806 patients, ASSET[16] (Anglo-Scandinavian Study of Early Thrombolysis) 5009 patients, and ISIS-2[12] 17 187 patients. The techniques and attitudes necessary for the organisation of multicentre international trials were now in place, and trial size as such was clearly not a problem.

Comparison of thrombolytic agents

The next logical step was to compare thrombolytic agents, even though the similar results obtained when streptokinase and alreplase were compared with placebo suggested that the effects of these agents might be very similar. The initial comparison, GISSI-2[17] (12 409 patients), was "too small" to have good power to detect a difference of 1% in the absolute mortality rates of the two agents (the best that could be expected) and so was enlarged by the addition of an international section,[18] making a total of 20 891 patients. Streptokinase and alteplase gave similar results but the trial was immediately criticised because the use of heparin might not have been optimal. ISIS-3[19] (38 574 patients) confirmed that streptokinase and alteplase had a similar effect on mortality, and also that anistreplase (APSAC), which in its initial mini-trial (1258 patients) had shown the greatest improvement in survival rate compared with placebo,[20] had an identical effect. Once again, however, doubts were expressed about the optimal use of heparin, and hence the 40 000 patient GUSTO Study.

This story of ever-increasing trial size is largely attributable to the willingness of the pharmaceutical industry to fund trials that might be expected to sell its products. The interest of industry has extended to problems such as the place of angioplasty after thrombolysis,[21 22] but without industrial support it has not been possible to answer questions such as whether the effect of β blockers and aspirin are additive. The problem remains how to answer such questions with lower funding and smaller patient groups, and various models have been proposed.

Alternative trial options

FACTORIAL DESIGN

An attractive possibility is that of the factorial design, in which two (or even three) treatments are compared with placebo by independent randomisation within one trial umbrella. This worked well in ISIS-2, which allowed the effect of aspirin to be studied together with streptokinase without the expense of an independent trial. However, these designs are only fully effective when there is no interaction between the two agents, and in the GISSI-2 International Study[18] it seemed that there was such an interaction between the effect of alteplase and heparin. Multifactorial designs are, in fact, something of a gamble.

META-ANALYSES

Meta-analyses of many trials, each of them on its own inadequate, is sometimes held out as a substitute for a single adequate trial. However, while meta-analyses can give an overall answer such as "antiplatelet agents reduce fatality in patients with vascular disease", or "β blockers reduced fatality after myocardial infarction", they can never tell a clinician which antiplatelet agent or β blocker, in what dose, to give to any particular patient. Meta-analysis can provide a theoretical background against which to plan further trials, but not much more.

SUB-SET ANALYSES

Sub-set analyses within individual trial results have at times been used instead of additional prospective trials to identify patients who are most likely to benefit from a particular treatment, but it is now accepted that such analyses should be used with extreme caution and are more likely to be misleading than helpful.

SURROGATE END POINTS

This leaves the surrogate end point for the poor man's clinical trial. The strategy is to identify some aspect of the patient's response that is amenable to precise measurement and is also correlated with the end point of interest. As an example, left ventricular dilatation is correlated with one month mortality after myocardial infarction. If a treatment can be shown to reduce left ventricular diltatation, then it is argued that such a treatment will also save lives. The fallacy of such arguments has been shown in the various lipid-lowering trials, all of which failed to demonstrate the fatality reduction that was assumed would go hand in hand with a reduction in plasma cholesterol.[23-26] Similarly with high blood pressure: the ability of a drug to lower pressure could be taken as a surrogate for mortality reduction, on the assumption that the effects of propranolol and bendrofluazide shown in the MRC trial[27] (17 345 patients) could be extrapolated to all other hypotensive agents. The PACK (Prevention of Atherosclerotic Complications with Ketanserin) trial in 3899 patients with peripheral vascular disease[28] put an end to this convenient theory, for this study showed that a drug of proven hypotensive efficacy could under certain circumstances be dangerously arrhythmogenic.

MEGA-TRIALS

It seems then that there is little alternative to the mega-trial for comparing the efforts of two or more agents, particularly when, as with myocardial infarction, there is little scope for further reductions in mortality. Certainly, when there are theoretical or laboratory based reasons to suppose that a new drug in a particular class would reduce mortality more than an older drug of that type, a comparative trial can be set up if the manufacturer is prepared to pay for it. CAPRIE (Clopodogrel v Aspirin in Patients at Risk of Ischaemic Events) is an example of this: it has been decided to set up, as the first major trial of this new antiplatelet agent, a comparison with aspirin in 15 000 patients with coronary, cerebral, or peripheral vascular disease. This is an expensive and commercially high-risk undertaking, but it is probably the only way to find out whether such a drug has a clinical role.

The problem is slightly different when a completely new class of drug appears for the treatment of a condition for which there is already established therapy—for example, the phosphodiesterase inhibitors for the treatment of heart failure. Under these circumstances withholding the established treatment (in the case of heart failure, an angiotensin converting enzyme inhibitor[29 30]) is unethical and the new therapy has to be added to the old. The chances of achieving a further large reduction in fatality by such an addition are inevitably small, and the risk that the clinical trial programme will fail to show a benefit is high. In a sense the demonstration in the PROMISE (placebo controlled survival study of oral milrinone in severe heart failure) trial that milrinone increased fatality[31] was useful in eliminating this drug, but suppose its effect had been neutral? Would this have implied that milrinone was of no use? After all it had clearly been shown effective in short-term intravenous studies.

The future

Clearly there will always be a need for new drugs. Ideally they will be more effective, but in most cases their value will be for individual patients who fail to respond to established therapy, or who are for some reason intolerant of it. If a new drug is only to be licensed if it has been shown in a mega-trial to be superior to its predecessor, then the introduction of compounds must inevitably be inhibited. The cost of the trial itself, taken in context of a likely result, would become an unrealistic financial risk even for the largest pharmaceutical company. For treatments without pharmaceutical backing—for example, comparison of coronary artery bypass grafting and percutaneous transluminal coronary angioplasty such as are being made in the RITA (Randomised Intervention Treatment of Angina) Trial[32]—mega-trials are already an impossibility. We need to change prevailing attitudes to the evaluation of treatments to one that recognises the value of information already collected and appreciates the nature of clinical decision-making. In particular, we need to develop further the concept of equivalence of medical therapies. All too often, the issues of treatment equivalence and the problem of interpreting a negative trial have been confused. When the difference in expected benefit to the patient is of no practical importance, it does not matter if a small treatment difference is missed.

Alternative approaches

One possible approach involves a re-examination of the place of the uncontrolled study that uses data from another source as the comparator. Arguments against the use of historical controls emphasise the potential sources of bias inherent in this approach.[33] It may be difficult to ensure that the treatment groups are truly comparable, or that ostensibly similar data—disease history or concurrent therapy, etc—have been recorded in a similar manner. Finally, developments in clinical practice between the collection of the control data and the data pertaining to the new therapy may be important. These concerns are important, but do not automatically rule out the use of historical data especially in those areas where mega-trials are now contemplated. Consider the introduction of a new thrombolytic agent, which may have the potential for fewer side effects or benefit of a reduced cost. Superiority over existing agents is not expected. However, we now know so much about the effect of streptokinease and alteplase in patients with myocardial infarction from the previously completed trials where the patient populations have been clearly identified, that we should perhaps be prepared to set limits in respect of efficacy and safety that the new product should satisfy and allow an open study to determine whether these limits can be satisfied.

Trials to show the equivalence of two therapies are not new.[34 35] It has been argued that the sample size for such studies should be determined with reference to a confidence interval for the difference in the efficacy of the two therapies. One requires that in the event that the study shows that the two treatments are similar, the confidence interval for the difference should be acceptably "small". Others have argued that in addition sequential methods should be used, with recruitment to a trial stopped when it is clear that that treatment effects are sufficiently close to be judged as equivalent.[36 37] However, there is as yet little agreement on how to define equivalent therapies and cautious definitions lead yet again to large trial sample sizes.

Equivalent therapies are not necessarily identical therapies. The clinician choosing between two alternative therapies is making a decision. He is conscious of the benefits of a good outcome and of the costs or "losses" of a bad outcome. Decision theory[38] provides a framework for analysing such decisions, and within this framework equivalent therapies are clearly those where the expected gains or losses associated with one therapy compared with another are not considered to be clinically important. Clinical trials allow one to estimate the probabilities associated with each distinct outcome for each treatment. However, in many situations the costs assigned to the various outcomes may be such that the probabilities need be known only imprecisely for equivalence to be accepted. Large trials may not be necessary.

For complete certainty about the relative effect of one drug compared with another there is no alternative to the mega-trial. Where the pharmaceutical industry sees it to be in its commercial interests the mega-trial will doubtless continue. But this may mean that minor improvements in drug development are missed because they are commercially non-viable. We may have to learn to quantify better the costs and benefits of therapies and live with a little uncertainty if we are to progress.

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Changes in left ventricular function and wall thickness in heart transplant recipients and their relation to acute rejection: an assessment by digitised M mode echocardiography

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Abstract

***Objective*—Assessment of changes in left ventricular diastolic function and wall thickness after heart transplantation to verify whether these changes predicted acute rejection assessed by endomyocardial biopsy.**

***Design*—Follow up according to a predefined protocol of consecutive patients from the first week after transplantation.**

***Setting*—Heart transplantation unit of the Thoraxcentre, University Hospital Rotterdam Dijkzigt, The Netherlands.**

***Patients*—All 32 patients undergoing orthotopic heart transplantation from 1 January 1989 to 31 March 1990 were examined. Two were excluded from the analysis. Patients were treated with cyclosporin and low dose steroids.**

***Main outcome measures*—Data obtained by digitised M mode echocardiography were compared with the results of endomyocardial biopsy (Billingham classification). Mean values for left ventricular wall thickness, internal dimension, and their standardised rates of change and fractional shortening were determined from 4–6 consecutive expiratory beats. Mean values and individual trends during follow up were also investigated for each ultrasound variable. The results of these average values were compared with values in a group of 10 healthy volunteers.**

***Results*—Median follow-up was 177 days (range 10–399). Two hundred and sixty three consecutive M mode studies were examined in relation to concurrent biopsy results. No significant differences were observed between the ultrasound variables at the time of moderate acute rejection (Billingham class 2, n = 37) and other biopsy classes (n = 226). Nor did changes in individual patients predict (moderate) acute rejection episodes. Twenty six of the 30 patients had an abnormal (slow) left ventricular relaxation pattern throughout follow up.**

***Conclusions*—Digitised left ventricular M mode echocardiography did not predict the presence of acute rejection. In most patients there was a persistent slow left ventricular relaxation pattern.**

(*Br Heart J* 1992;68:356–64)

Systolic and diastolic left ventricular function and wall thickness in patients after heart transplantation may be altered by perioperative ischaemia and subsequent reperfusion damage, by acute and chronic rejection, and by postoperative systemic hypertension. Early studies suggested that increases in wall thickness or left ventricular mass shown by digitised M mode echocardiography are moderately reliable markers of acute rejection in recipients of orthotopic heart transplants treated with azathioprine and prednisone immunosuppression.[1–2] In another study digitised M mode echocardiography showed deterioration of diastolic left ventricular function in similarly treated patients.[3] The clinical and haemodynamic signs of acute rejecton differ considerably in patients treated with cyclosporin/prednisone and those treated with azathioprine/prednisone.[4] With cyclosporin/prednisone the onset of acute rejection is more insidious with less pronounced functional and structural changes in the heart during early stages of acute rejection.[4 5] In two recent studies significant increases in left ventricular wall thickness (septum and posterior wall) and calculated left ventricular mass were found during moderate acute rejection (sensitivity 61% and 69%) in patients treated with cyclospin/prednisone.[6 7] In three other studies, however, no increase in wall thickness or deterioration of systolic function (peak shortening rate of the left ventricular internal dimension) was seen during moderate acute rejection in similarly treated patients.[8–10] Because of these conflicting results we prospectively studied digitised left ventricular M mode echocardiograms in patients between one week and six months after transplantation.

Patients and methods

All 32 consecutive patients undergoing orthotopic heart transplantation during 1989 were enrolled into an observational unrandomised prospective study between January 1989 and March 1990 with serial follow up of consecutive patients according to a predefined protocol. For the detection of acute rejection by M mode echocardiography each patient served as his own control and was followed up systematically from the first week after transplantation. Maintenance immunosuppressive treatment was cyclosporin and low dose prednisone. All patients were in sinus rhythm. Endomyocardial biopsy specimens for routine monitoring of acute rejection were taken at least 15 times in the first year according to a predefined protocol. Biopsy specimens were graded according to the Billingham classification.[5 11] Biopsy specimens were taken every week for the first six weeks after heart transplantation. Thereafter they were taken during weeks 8, 10, 14, 18, 24, 30, 38, 46, 52. Extra biopsies were performed in between these times if there was a clinical suspicion of acute rejection. In cases of moderate acute rejection (Billingham class 2) anti-rejection treatment was given (intravenous methylprednisolone or rabbit anti-thymocyte globulin). The globulin was given when moderate acute rejection occurred in the first two months after transplantation or when there was continuing moderate acute rejection despite previous anti-rejection treatment. In all other cases intravenous methylprednisolone was given. A biopsy was performed one week after the end of anti-rejection treatment.

Ultrasound recordings were obtained within six hours of biopsy. M mode tracings were recorded and analysed by one observer without prior knowledge of the biopsy results. Simultaneous cross sectional echocardiograms and left ventricular M mode studies were obtained from the parasternal long axis view with either a 3·75 or 2·25 MHz focused precordial transducer (Toshiba SSH-160 A). The patients were in the supine left lateral position with the transducer placed in the second to fourth left intercostal spaces. Care was taken to direct the M mode cursor perpendicularly to the left ventricular long axis at the level of the chordal attachments to the mitral valve. Tracings were recorded at a paper speed of 100 mm/s in combination with an electrocardiogram, phonocardiogram, and a respiratory tracing (based on changes in thoracic impedance). End diastole was taken as the onset of the first heart sound (mitral valve closure) and this was confirmed by the end of the mitral flow signal on a concurrent pulsed wave transmitral Doppler study. End systole was derived from the onset of the second heart sound on the phonocardiogram (A2, verified by recording an M mode echocardiogram of aortic valve closure). Figure 1 shows an example of the characteristic left ventricular M mode recording obtained during the study with its corresponding digitised tracing. Off-line, 4–6 consecutive end expiratory beats were analysed with a software program developed in our laboratory. Similar analysis programmes were used by others.[3 12] Care was taken to avoid artefacts in the M mode measurements of the septum and posterior wall caused by chordae, papillary muscle, or pericardial effusion. This was done with close reference to videotaped simultaneous cross sectional echocardiograms. Wall thickness and internal dimensions were measured from leading edge to leading edge. The following variables were measured: IVSd and IVSs = wall thickness of the interventricular septum at end diastole and end systole (cm); LVPWd and LVPWs = wall thickness of the left ventricular posterior wall at end diastole and end systole (cm); TWT = total diastolic wall thickness (cm), which is the sum of IVSd + LVPWd; LVd and LVs = left ventricular internal dimension at end diastole and end systole (cm); MWTCR = mean wall thickness cavity ratio, which is the sum of IVSd + LVPWd divided by two and again divided by LVd (synonym: wall thickness index); VCF = peak shortening rate of the left ventricular internal dimension (cm/s); LVSR = peak shortening rate of the left ventricular internal dimension and LVLR = peak lengthening rate of left ventricular internal dimension, both standardised for instantaneous left ventricular internal dimension (s^{-1}); and PWTkR = peak rate of left ventricular posterior wall thickening (s^{-1}) and PWTnR = peak rate of left ventricular posterior wall thinning (s^{-1}), both standardised for instantaneous left ventricular posterior wall thickness.[3 12] In addition the percentage fractional shortening of the left ventricular diameter was calculated as ((LVd − LVs)/LVd × 100), in which LVd and LVs are the end diastolic and end systolic left ventricular internal dimensions. From the QRS complexes the RR interval and heart rate were calculated. Results for all variables are expressed as the mean value of the 4–6 end expiratory consecutive beats measured. Longitudinal follow up was assessed by measuring the differences in M mode variables between two consecutive examinations of the same patient. Thus the mean values of the actual examination minus the mean values of the previous examination were related to the concurrent transition from one biopsy class to another (Billingham classification).

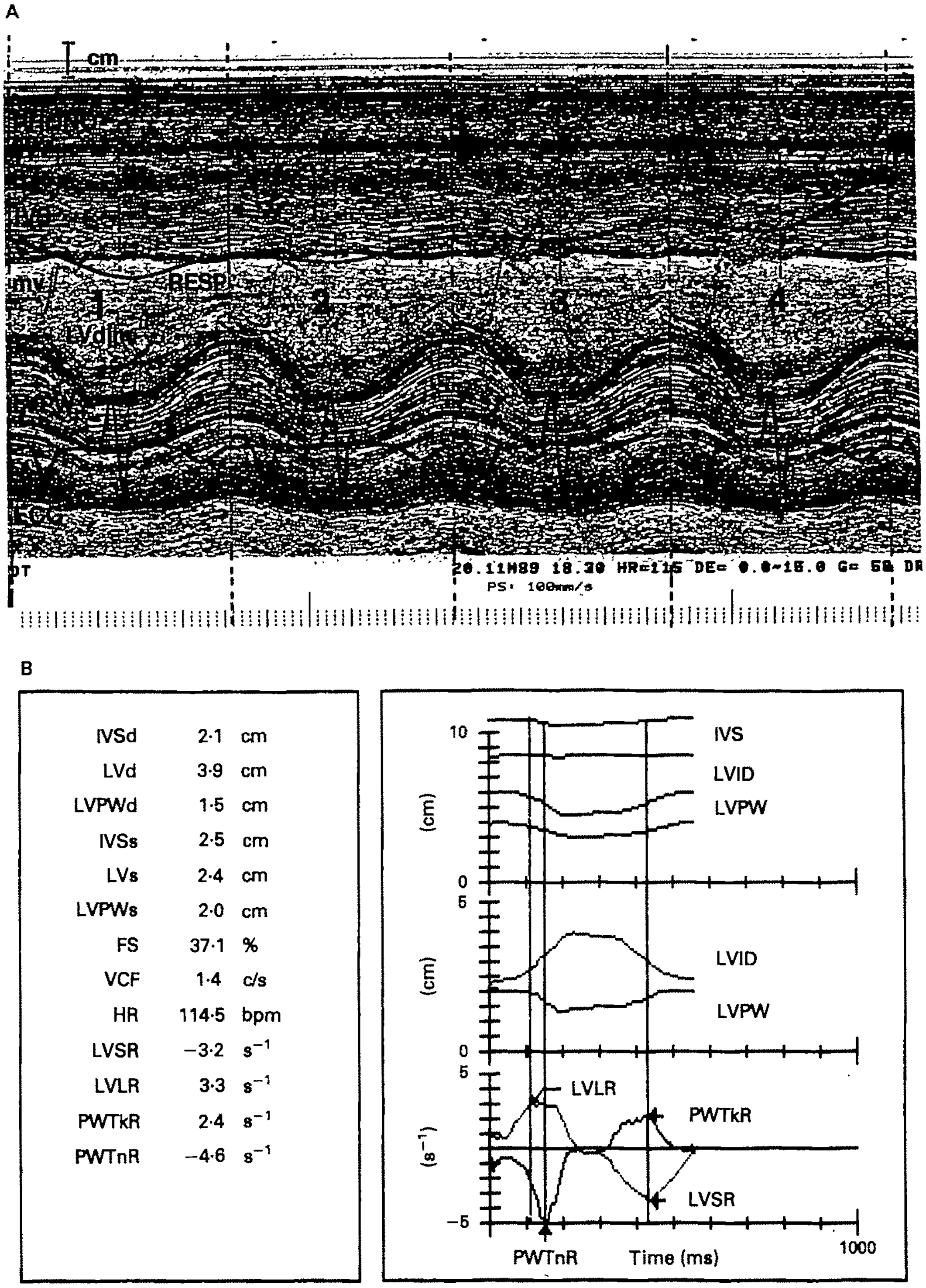
The trough concentration of plasma cyclosporin (ng/ml) was measured by a specific monoclonal radioimmunoassay[13] on the same day as the endomyocardial biopsy and echocardiographic examinations. Brachial cuff blood pressures (mm Hg) were measured on the same day.

The controls were 10 healthy volunteers (seven men and three women, mean (SD) age 29·6 (4·5) years) without any symptoms or signs of heart disease and with normal electrocardiograms.

Reproducibility was assessed by an intra and inter observer variation test for which 120 beats in 25 M mode recordings of different patients were reanalysed by either the same or a different observer.

DATA ANALYSIS

Intra and inter observer variations were determined by linear regression. The random errors were calculated by dividing the standard devia-



IVSd	2·1	cm
LVd	3·9	cm
LVPWd	1·5	cm
IVSs	2·5	cm
LVs	2·4	cm
LVPWs	2·0	cm
FS	37·1	%
VCF	1·4	c/s
HR	114·5	bpm
LVSR	−3·2	s^{-1}
LVLR	3·3	s^{-1}
PWTkR	2·4	s^{-1}
PWTnR	−4·6	s^{-1}

Figure 1 (A) Left ventricular M mode echocardiogram at paperspeed 100 mm/s PHONO, phonocardiogram; IVS, interventricular septum; LV dimension, left ventricular internal dimension; RESP, respiratory curve (trough in expiration); LVPW, left ventricular posterior wall; ECG, electrocardiogram; mv, mitral valve; S1, onset of the first heart sound (mitral closure); S2, onset of the second heart sound (aortic closure). Sometimes the onset of S1 was not clear in every beat (as in beat 2 and 4). In these cases the timing of mitral valve closure by transmitral pulsed wave doppler was calibrated with the QRS complex (in this case the nadir of the S wave on the ECG). (B) Continuous plot of the digitised contours of the interventricular septum, the left ventricular minor axis dimension, and the left ventricular posterior wall. The rates of change of the two left ventricular indices were obtained by differentiation. The vertical lines coincide with the peak rates of change. PWTnR and PWTkR are the peak posterior wall thinning and thickening rates both standardised for instantaneous posterior wall thickness. LVSR and LVLR are the peak shortening and peak lengthening rates, respectively, of left ventricular internal dimension, both standardised for instantaneous left ventricular internal dimension.

tion by the square root of the number of consecutive beats analysed ($\sqrt{4}$). One way analysis of variance (Scheffé's test) was used to compare the mean values of M mode variables or their individual differences, plasma cyclosporin concentrations, and blood pressures for the three biopsy classes. Linear regression was used to describe trends in time after cardiac transplantation for the M mode varables studied. The derived individual slopes of the regression equations were tested for significance by a paired Student's t test. Linear regression was also used to relate the wall thickness variables to left ventricular function. Similarly, duration of ischaemic time was related to various indices (averaged serial measurements in each patient). The Mann-Whitney U test was used to test the averaged serial values of patients against values obtained in healthy volunteers.

Results

Table 1 shows the results for the intra and inter observer variation test. Two of the 32 patients were excluded from the analysis: one because no satisfactory M mode readings could be obtained and the other because of prolonged septicaemia (two weeks), which is known to influence cardiac diastolic function.[14] The

Table 1 Intra and inter observer variation in patients after heart transplantation

M mode index	*Variation (±)*	
	Intra	*Inter*
HR (/min)	0·50	0·55
IVSd (cm)	0·04	0·04
IVSs (cm)	0·08	0·08
LVPWd(cm)	0·07	0·08
LVPWs (cm)	0·09	0·09
LVd (cm)	0·07	0·08
LVs (cm)	0·09	0·10
TWT (cm)	0·08	0·09
MWTCR	0·10	0·11
FS (%)	1·9	2·4
VCF (cm/s)	0·08	0·10
PWTKR (s^{-1})	0·36	0·34
PWTNR (s^{-1})	0·40	0·45
LVSR (s^{-1})	0·26	0·29
LVLR (s^{-1})	0·29	0·28

Measurement variability analysed over 120 beats in 25 patients, expressed as random errors. See text for abbreviations.

remaining patient group consisted of 25 men and five women (mean (SD) age 43 (12) years). The duration of ischaemia for the donor heart (interval between cross clamping of the aorta in the donor and reperfusion in the recipient) was 161 (41) minutes. Two patients originally treated with cyclosporin/prednisone were given azathioprine from 28 and 40 weeks after cardiac transplantion, because they had several acute rejection episodes (Billingham class 2). Twenty nine of the 30 patients survived until the end of the follow up (median 177 days, range 10–399) after transplantation). One patient died 10 days after transplantation of severe acute rejection which was confirmed at necropsy. Only one M mode recording had been obtained in this patient, a day before his death. At that time the biopsy specimen showed only mild acute rejection (Billingham class 1). The corresponding left ventricular M mode echocardiogram showed that the internal dimension and wall thickness were normal, as was systolic function. Diastolic function, measured by peak posterior wall thinning rate was slightly abnormal.

At the end of the study a total of 263 biopsy results with concurrent M mode recordings were available for analysis. The mean number of endomyocardial biopsy specimens and concurrent M mode studies per patient was assessed for several intervals after transplantation. From 0–6 weeks this was 3·8; from 6–12 weeks 1·7; from 12–26 weeks 2·3; and after 26 weeks it was 1·1. The number of ultrasound examinations at these times were 113, 50, 68, and 32 respectively. Overall 8·8 M mode studies per patient were available for analysis. For each patient the serial measurements of left ventricular wall thickness and internal dimension and function during individual follow up were averaged. The means from the remaining 29 patients were pooled to give a group mean value (table 2). In patients the wall thickness of the interventricular septum and posterior wall and mean wall thickness to cavity ratio were considerably increased, whereas the left ventricular internal dimension was smaller than in the controls and in published reports.[3 15 16] Systolic function, as judged by the peak posterior wall thickening rate, was depressed but not as judged by left ventricular shortening rate or fractional shortening. The greatest abnormality, however, was seen in diastolic function. The peak posterior wall thinning rate was clearly abnormal in all but four patients (table 2 and fig 2). The peak rate of left ventricular lengthening was not significantly different from normal. Only four of 29 patients had a peak posterior wall thinning rate in the normal range for the healthy volunteers. For the remaining 25 the increased left ventricular wall thickness together with the decreased absolute values of peak posterior wall thinning rate were consistent with a slow relaxation associated with left ventricular hypertrophy.[12] The latter is defined as IVSd > 1·2 cm and/or LVPWd > 1·1 cm.[15] According to this definition, and with some allowance for the measurement variability in our study (IVSd > 1·24 cm and LVPWd > 1·17 cm), hypertrophy of the septum was present in 101 (38·4%) out of 263 records, and hypertrophy of the posterior wall in 191 (72·6%) out of 263 records. The combination of both septal and posterior wall hypertrophy was seen in 85 (32·3%) out of 263.

We analysed trends in time for all variables in 27 of the 29 patients. Two patients had to be excluded, because each had only two recordings. Linear regression analysis showed no trend in any of the variables studied. The relaxation abnormality persisted in 22 patients without a clear tendency towards improvement during follow up. In the remaining five there was a tendency towards improvement of peak posterior wall thinning rate (those with sig-

Table 2 Comparison of mean values in 30 patients during serial follow up and values for 10 controls

	LVd	*IVSd*	*LVPWd*	*FS*	*LVSR*	*PWTKR*	*LVLR*	*PWTNR*
Patients:								
Mean (SD)	4·1 (0·3)	1·2 (0·2)	1·3 (0·2)	37 (7)	−2·8 (0·7)	2·6 (0·4)	3·6 (0·8)	−3·8 (0·8)
Median	4·1	1·2	1·3	35	−2·7	2·5	3·3	−3·5
Range	3·3 to 4·8	0·9 to 1·7	1·1 to 1·6	26 to 55	−5·0 to −1·9	1·9 to 3·4	2·5 to 5·7	−5·7 to −2·8
Controls:								
Mean (SD)	4·8 (0·3)	1·0 (0·1)	0·8 (0·2)	37 (3)	−2·4 to 0·4	3·5 (1·0)	3·3 (0·6)	−7·1 (2·5)
Median	4·8	1·0	0·8	37	−3·4	3·3	3·4	−5·9
Range	4·3 to 5·1	0·8 to 1·1	0·4 to 1·0	30 to 43	−2·4 to −4·1	2·0 to 5·6	2·4 to 4·1	−12·1 to −4·5
p*	$<10^{-4}$	$<3{\cdot}10^{-3}$	$<3{\cdot}10^{-6}$	NS	NS	$<2{\cdot}10^{-3}$	NS	$<3{\cdot}10^{-5}$

LVd, end diastolic left ventricular internal dimension (cm); IVSd, end diastolic septal thickness (cm); LVPWd, end diastolic thickness of left ventricular posterior wall (cm); FS, fractional shortening (%); LVSR, peak left ventricular shortening rate; LVLR, peak left ventricular lengthening rate (s^{-1}); PWTKR, peak posterior wall thickening rate; PWTNR, peak posterior wall thinning rate (s^{-1}). All rates are standardised for instantaneous left ventricular internal dimension or posterior wall thickness.

*Patients *v* controls.

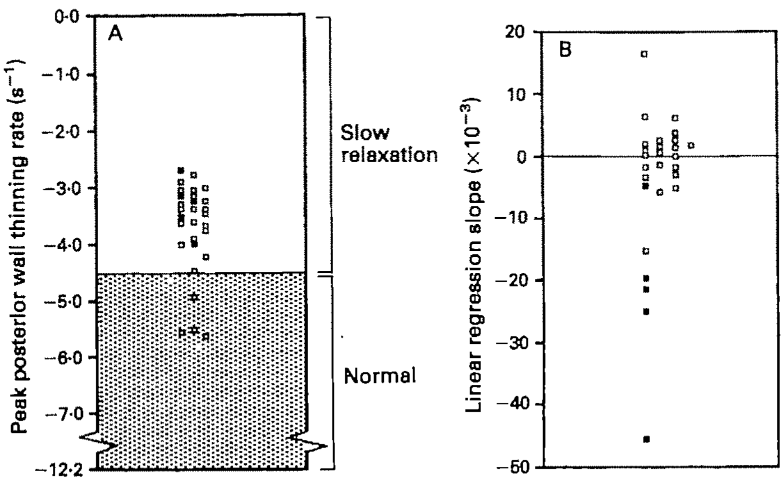


Figure 2 (A) Averaged serial data of peak posterior wall thinning rate for 29 patients. A patient who died and two others have been omitted. The normal range is indicated (range −12·2 to −4·5 s^{-1}). Twenty five patients had values outside the normal range and showed a slow left ventricular relaxation pattern. (B) Linear regression slopes of peak posterior wall thinning rate for 27 of the 29 patients. The group showed no significant trend for this index. Only five patients had significant negative slopes (black squares) and thus showed a tendency towards an improvement in their slow relaxation pattern. Regression slopes for the other patients were not statistically significant.

nificant negative slopes in fig 2). There was an inverse relation between individual averaged peak posterior wall thinning rate and the duration of ischaemic time (fig 3).

Peak posterior wall thickening and thinning rates correlate inversely with end diastolic posterior wall thickness. Therefore increased wall thickness contributes to the pattern of slow left ventricular relaxation. Figure 4 shows a linear regression plot for the correlation between left ventricular posterior wall thickness (measured in diastole (LVPWd) and peak posterior wall thickening (PWTkR) and thinning rates (PWTnR).

Correlations between blood pressure measurements and M mode indices of wall thickness and left ventricular function were generally poor. Therefore, instantaneous blood pressure did not exert an important influence on the results of this study.

Table 3 shows the ultrasound indices of left ventricular wall thickness, internal dimension, and systolic and diastolic function grouped according to the concurrent biopsy class. In patients with biopsy class 0, interventricular septal wall thickness (either at end diastole or end systole) was increased. In the pooled data for the other indices no significant differences were seen. Trough concentrations of plasma cyclosporin, heart rate (sinus tachycardia), and blood pressure were similar in all biopsy classes. Biopsy classes could not be discriminated on the basis of indices of systolic or diastolic function.

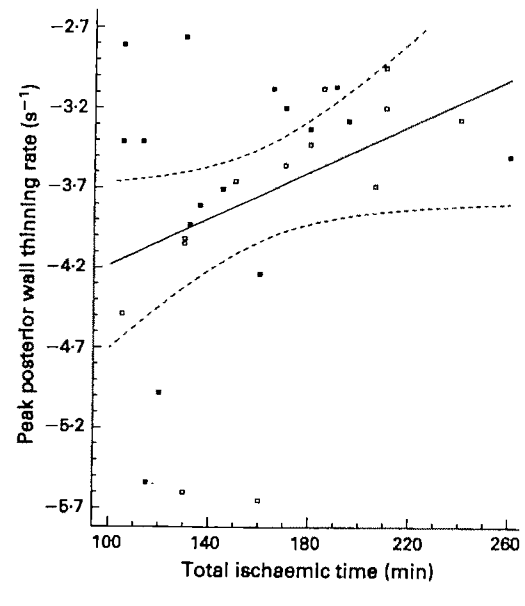


Figure 3 Relation between mean serial values of peak posterior wall thinning rate and the total duration of ischaemic time for each of the 29 patients. Linear regression model: $Y = a + bX$; a (intercept) = −4·90; b (slope) = 0·0072; correlation coefficient = 0·37. Linear regression showed a significant trend for the absolute value of this index to decrease as the ischaemia time increased. The 95% confidence interval of the regresson line is shown.

Table 4 shows the pooled data of individual changes in M mode variables, grouped according to transitions from one biopsy class to another (in total 234 transitions). For all ultrasound variables studied there were no significant differences between the pooled data of several clinically important transitions from one histological group to another. Therefore, this method did not allow diagnosis of moderate acute rejection either. The large standard deviations in tables 3 and 4 show that there is a wide overlap between biopsy classes. Figure 5 gives an example of an individual plot for various M mode variables versus follow up time. In this patient the first moderate acute rejection episode did not coincide with an absolute low value of peak posterior wall thinning rate whereas the second one did. These low values for posterior wall thinning rate, however, were not specific for moderate acute rejection. Similarly, changes in the other M mode indices during acute rejection episodes were not specific either.

Discussion

The aim of this prospective study was to assess a possible trend with time in left ventricular systolic and diastolic function and wall thickness in recipients of orthotopic heart transplants and to verify whether changes related to rejection could be detected by ultrasound. Digitised left ventricular M mode echocardiography was used because it provides quantitative information on wall thickness, left ventricular dimension, and systolic and diastolic function, including rates of left ventricular posterior wall thinning and thickening. These variables have been reported to be sensitive markers of diastolic and systolic function.[3 12 17]

REPRODUCIBILITY OF M MODE VARIABLES

The results indicate that the reproducibility of the variables left ventricular dimension and wall thickness (expressed as random errors) was good and that it was acceptable for the ratio of mean wall thickness to cavity and standardised rates of change. The latter are clearly influenced by the standardisation for instantaneous posterior wall thickness or instantaneous left ventricular internal dimension. Therefore the error in peak VCF is much smaller than that of peak left ventricular shortening rate, which is standardised to the instantaneous left ventricular internal dimension.

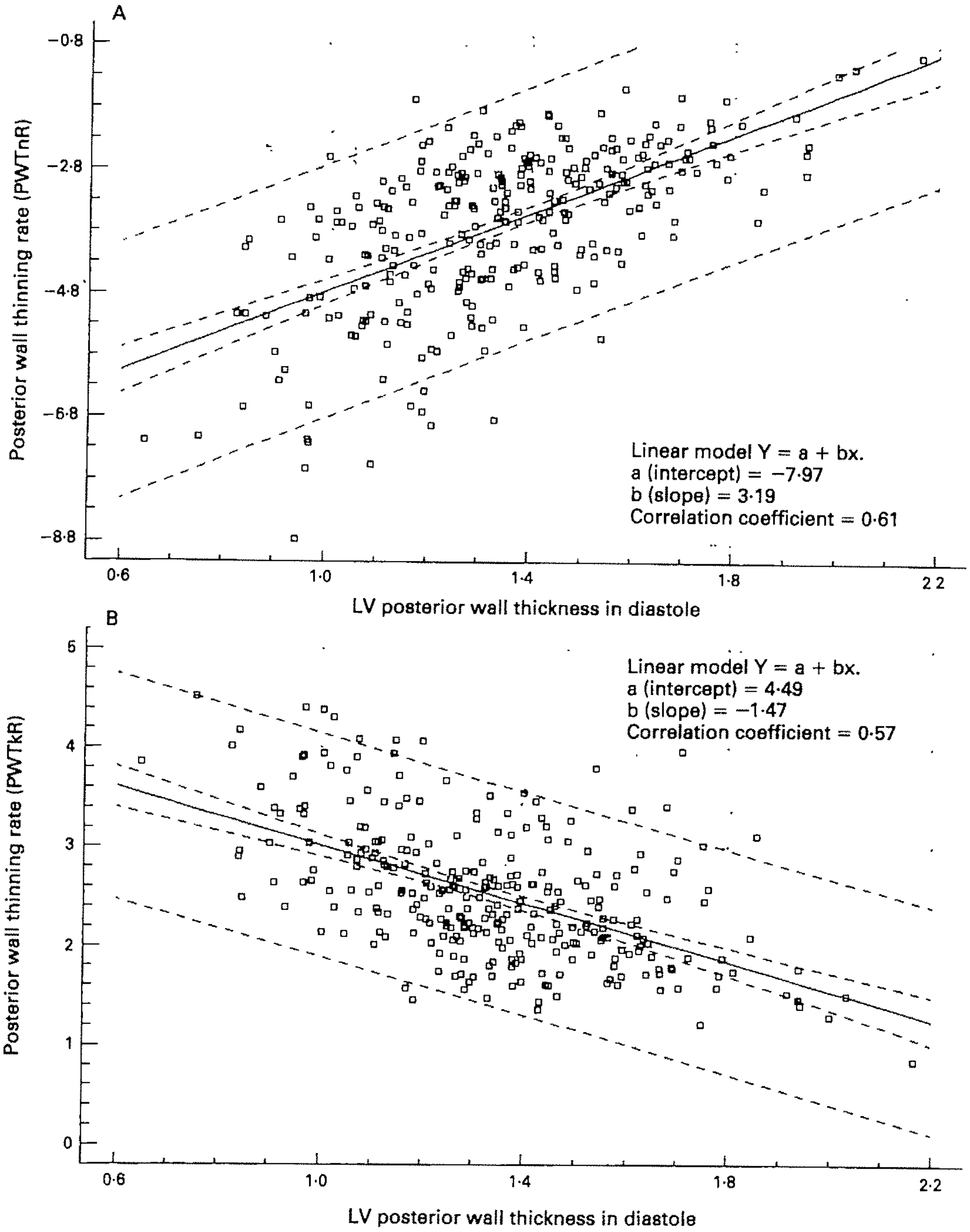


Figure 4 Linear regression of (A) peak posterior wall thinning rate (PWTnR) and (B) peak posterior wall thickening rate (PWTkR) on diastolic thickness of the left ventricular posterior wall (LVPWd). The corresponding linear regression equations are indicated. The inner broken lines are the 95% confidence intervals of the linear regression line and the outer broken lines are the 95% prediction limits for any given values of PWTnR, PWTkR, and LVPWd.

SLOW LEFT VENTRICULAR RELAXATION PATTERN

Wall thickness was increased and both the left ventricular internal dimension and peak posterior wall thinning rate were decreased in all patients whether or not they showed evidence of acute rejection. This result indicates a slow left ventricular relaxation pattern associated with left ventricular hypertrophy that persisted during follow up in 22 out of 27 patients. These data were compared with another study of left ventricular digitised M mode echocardiography in patients with non-obstructive hypertrophic cardiomyopathy in association with long-standing hypertension and in patients with cardiac amyloidosis.[12] The left ventricular wall thickness and peak posterior wall thinning rates in our patients were typical of the group with hypertension. The data on left ventricular internal dimension, however, resembled those obtained in patients with restrictive cardiomyopathy caused by cardiac amyloidosis. Increased myocardial stiffness or signs of a restrictive physiology were reported by others using M mode echocardiography and cardiac catheterisation,[18] serial right heart catheterisation,[19] or pulsed wave transmitral Doppler.[20] This slow relaxation/restrictive filling pattern may be caused by fibrosis and persistent cellular infiltration and oedema (that is, mild acute rejection) within the myocardium or by left ventricular hypertrophy caused by systemic hypertension. All these factors tend to increase wall thickness and have a negative effect on both systolic and diastolic function, as illustrated by the inverse relation between the rates of diastolic wall thickness and posterior wall thinning and thickening (fig 4). Furthermore, impairment of the passive diastolic properties of the left ventricle was reported to correlate with the ischaemic time of the donor heart, even if

Table 3 M mode indices in various Billingham classes (mean (SD)

	*Class 0 (n = 49)**	*Class 1 (n = 177)**	*Class 2 (n = 37)**
Plasma cyclosporin (ng/ml)	154 (172)	130 (66)	141 (80)
Systolic blood pressure (mm Hg)	144 (21)	143 (15)	141 (16)
Diastolic blood pressure (mm Hg)	96 (13)	95 (11)	93 (13)
Heart rate (beats/min)	92 (13)	94 (10)	97 (12)
End diastolic indices:			
Mean wall thickness cavity ratio	0·3 (0·1)	0·3 (0·1)	0·3 (0·1)
Total wall thickness (cm)	2·6 (0·4)	2·5 (0·4)	2·5 (0·4)
Interventricular septum† (cm)	1·3 (0·3)	1·2 (0·3)	1·2 (0·3)
Left ventricular internal dimension (cm)	4·2 (0·5)	4·2 (0·4)	4·0 (0·4)
Left ventricular posterior wall (cm)	1·3 (0·3)	1·3 (0·3)	1·3 (0·3)
End systolic indices:			
Interventricular septum† (cm)	1·6 (0·4)	1·5 (0·3)	1·5 (0·3)
Left ventricular internal dimension (cm)	2·5 (0·5)	2·7 (0·5)	2·6 (0·4)
Left ventricular posterior wall (cm)	2·0 (0·3)	1·9 (0·3)	2 0 (0·4)
Indices of left ventricular function:			
Fractional shortening (%)	39·4 (9·2)	36·0 (9·0)	36·5 (9·3)
Peak VCF (cm/sec)	1·4 (0 3)	1·3 (0·4)	1·3 (0·4)
Peak left ventricular shortening rate (s^{-1})	−3·0 (1·1)	−2·7 (1·0)	−2·8 (0·9)
Peak left ventricular lengthening rate (s^{-1})	3·8 (1·1)	3·4 (1·0)	3·5 (1·0)
Peak posterior wall thickening rate (s^{-1})	2·7 (0·7)	2·5 (0·7)	2·6 (0·7)
Peak posterior wall thinning rate (s^{-1})	−3·9 (1·4)	−3·6 (1·3)	−3·8 (1·3)

*Number of echocardiographic examinations.
†$p < 0·05$ for differences between classes 0 and 1 for both end diastolic and end systolic thickness of the interventricular septum.

assessed one year after orthotopic heart transplantation.[18] This accords with our findings (fig 3).

DETECTION OF MODERATE ACUTE REJECTION

In the present study we detected no significant differences in left ventricular digitised M mode variables between moderate acute rejecton and its absence, either at group level or in individual patients. In this respect our data are consistent with three other studies in similarly treated patients.[8–10] The observed differences at group level between Billingham class 0 (no rejection) and class 1 (mild rejection) in both systolic and diastolic interventricular septal wall thickness are considered to be of no clinical importance and in individual patients did not reach significance when measured serially. Class 0 biopsy specimens were more common in the early postoperative period and the increased wall thickness in this biopsy class may be related to myocardial oedema caused by ischaemia and subsequent reperfusion injury. In contrast to other studies in cyclosporin treated patients[6 7] the calculation of total wall thickness (TWT) did not give better results than the measurement of either interventricular septal or posterior wall thickness. The explanation for this difference in results between our study and the studies mentioned for the detection of moderate acute rejection by measurement of total wall thickness may lie in left ventricular hypertrophy (especially of the posterior wall) and/or persisting cellular infiltration within the myocardium (Billingham class 1). In contrast to the two other studies both these factors were present in most of our patients. Increases in wall thickness caused by moderate acute rejection are harder to detect in the presence of these factors. We do not know whether the absence of left ventricular hypertrophy in the other two studies could be attributed to lower plasma concentrations of cyclosporin.

The considerable overlap of digitised M mode variables between biopsy classes and the fluctuations during individual follow up might be explained by the continuous interplay of changes in haemodynamic factors other than those associated with acute rejection, such as pulmonary hypertension; ischaemic injury and subsequent reperfusion injury with its associated oedema, which gradually diminish after transplantation; and the onset of hyper-

Table 4 Transition from one biopsy class to another with concurrent changes in digitised M mode indices

	Billingham class								
	0→1	*0→2*	*1→2*	*1→0*	*2→1*	*2→0*	*0→0*	*1→1*	*2→2*
N	25	5	27	24	30	2	13	104	4
HR	−0·1 (10)	−0·3 (11)	2 7 (8)	3·1 (6)	−0·6 (8)	−1·6 (2)	−2·5 (7)	0·6 (7)	−1·9 (13)
IVSd	−0·02 (0·18)	−0·05 (0·13)	0·02 (0·23)	0·01 (0·23)	0·01 (0·20)	−0·21 (0·42)	−0·06 (0·33)	−0 02 (0·19)	−0·01 (0·34)
IVSs	−0·01 (0·29)	0·04 (0·16)	0·03 (0·22)	−0·01 (0·25)	−0·02 (0·22)	0·15 (0·22)	−0·04 (0·35)	−0·01 (0·23)	0·16 (0·22)
LVPWd	0 (0·26)	−0·11 (0·25)	0·01 (0·27)	0·07 (0·24)	−0·01 (0·24)	−0·16 (0·35)	0·02 (0·28)	−0·02 (0·28)	−0·02 (0·21)
LVPWs	−0·04 (0·22)	−0·04 (0·20)	−0·03 (0·21)	0·10 (0·30)	−0·01 (0·33)	−0·53 (0·75)	0·04 (0·05)	−0·02 (0·29)	−0·03 (0·27)
LVd	−0·05 (0·39)	0·02 (0·46)	−0·09 (0·28)	−0·04 (0·42)	0·01 (0·34)	0·29 (0·55)	0·07 (0·14)	0·05 (0·44)	−0 07 (0·24)
LVs	0·10 (0·33)	0·06 (0 26)	0·09 (0·31)	−0·09 (0·43)	−0·09 (0·33)	0·39 (0·37)	−0·09 (0·42)	0·03 (0·45)	−0·35 (0·41)
TWT	−0·01 (0·32)	−0·24 (0·27)	0·01 (0·39)	0·08 (0·36)	0·02 (0·28)	−0·38 (0·76)	−0·05 (0·37)	−0·03 (0·35)	−0·03 (0·47)
MWTCR	−0·00 (0·05)	−0·04 (0·01)	0·01 (0·06)	0·01 (0·05)	0 00 (0·05)	−0·07 (0·14)	−0·01 (0·04)	−0·01 (0·06)	−0·00 (0·07)
FS	−3·1 (8·0)	−1·2 (2·0)	−3·7 (8·1)	1 8 (7·1)	2·7 (8·5)	−6·5 (2·7)	3·1 (10 2)	−0·2 (8·1)	7·7 (11·2)
VCF	−0·11 (0·28)	−0·13 (0·10)	−0·09 (0·30)	0·04 (0·28)	0·10 (0·36)	−0·30 (0·04)	0·08 (0·38)	−0·02 (0·32)	0·23 (0·35)
PWTKR	−0·14 (0·85)	0·12 (0·55)	0·12 (0·87)	0·09 (0·58)	−0·10 (0·87)	−0·50 (0·70)	−0·00 (0·30)	−0·02 (0·83)	−0 08 (0·58)
PWTNR	0·36 (1·44)	−0·58 (2·00)	−0·15 (1·42)	0·06 (1·19)	0·13 (1·35)	0·69 (1·03)	−0·14 (1·03)	−0·12 (1·40)	0·89 (1·48)
LVSR	0·16 (0·74)	0·28 (0·20)	0·26 (0·90)	−0·21 (0·66)	0·23 (1·09)	0·91 (0·61)	−0·30 (1·13)	0·08 (0·92)	−0·48 (0·91)
LVLR	−0·32 (0 94)	0·18 (0·85)	−0·25 (0·93)	0·34 (1·03)	0·16 (1·14)	−1·10 (1·37)	0·18 (1·22)	0·02 (1·06)	0·50 (1·27)

N, number of observations for transitions between biopsy classes. The mean differences (1 SD) are presented for several transitions. For abbreviations and units of measurement see text and other tables.

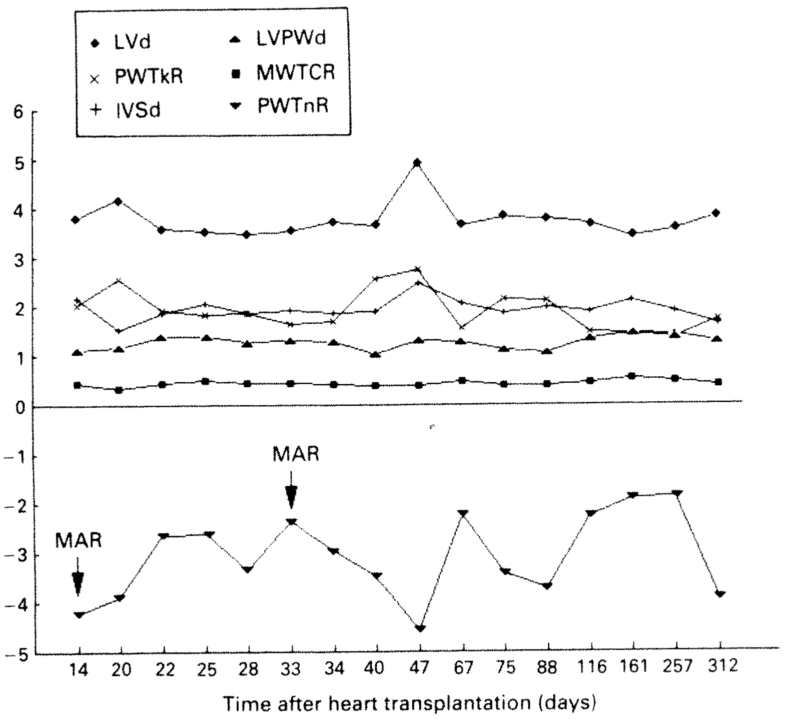


Figure 5 Trends in six left ventricular digitised M mode indices in one patient during follow up (days after transplantation). LVd, diastolic thickness of the left ventricular internal dimension; PWTkR, peak posterior wall thickening rate; IVSd, diastolic thickness of the interventricular septum; LVPWd, diastolic thickness of the left ventricular posterior wall; MWTCR, mean wall thickness cavity ratio; PWTnR, peak posterior wall thinning rate; MAR, moderate acute rejection.

tension induced left ventricular hypertrophy.[10] Finally, antihypertensive treatment, including diuretics, calcium antagonists, angiotensin converting enzyme inhibitors, other vasodilators, or sometimes β blocking agents, has a profound effect on loading conditions and the inotropic and lusiotropic states.[21]

It is unlikely that the overlap of M mode variables between biopsy classes is caused by false negative biopsy results because of sampling error, which is reported to be low (2 to 5%).[22] The plasma cyclosporin concentration was not lower in the acute rejection groups (biopsy classes 1 and 2) and therefore myocardial wall thickness (as a marker of myocardial tissue reactivity during acute rejection) was not dependent on the cyclosporin concentration. In our hospital, however, biopsy specimens are classified as "moderate acute rejection" requiring rejection therapy only if an interstitial cellular infiltrate together with myocyte necrosis is detected. Fibrosis and interstitial oedema, which may affect ventricular function, are often present in biopsy specimens classified as "mild acute rejection". Therefore it is not surprising that M mode indices of left ventricular systolic and diastolic function do not seem to be related to the histological classification.

LIMITATIONS OF THE STUDY

There were three. Firstly, we did not take account of the effects of recipient atrial contraction and relaxation, which may affect all parts of the cardiac cycle.[23] The recipient's atrial P waves on the electrocardiogram are objective criteria for the presence of recipient atrial contraction within the cardiac cycle.[23] In our experience recipient atrial P waves can only be seen in about 18% of all tracings despite the presence of very clear donor P waves. This means that in about 82% of all tracings we were unable to use an objective criterion for the presence of recipient atrial contraction. Furthermore, in pulsed wave transmitral Doppler studies of diastolic left ventricular function beat to beat variability induced by respiration may be larger than the variability induced by recipient atrial contraction, especially in patients with pericardial effusion.[23 24] To our knowledge there are no reports of the variability of digitised M mode indices but presumably the variability would be of a similar magnitude and direction as in pulsed wave transmitral Doppler studies. Because most of our patients had small to moderate pericardial effusions during follow up, respiratory induced variability must have been substantial. We reduced this major source of beat to beat variability by analysing 4 to 6 consecutive end expiratory beats.

Secondly, digitised left ventricular M mode echocardiography in fact only assesses the function of the basal portion of the left ventricle. Some degree of paradoxical septal motion was present in most of the patients, and could have influenced the indices measured by digitised M mode echocardiography although posterior wall dynamics are unlikely to have been affected by this phenomenon.

Thirdly, with left ventricular M mode echocardiography there will be pseudo-hypokinesis of the septum and pseudo-hyperkinesis of the left ventricular posterior wall affecting posterior wall dynamics, peak left ventricular lengthening and shortening rates and fractional shortening. This is inherent in any one dimensional technique with a fixed reference point, and is caused by the anterior motion of the entire heart relative to the transducer. The progressive restraining effect of postoperative adhesions reduces this anterior motion of the entire heart after the first postoperative months.[25] In the presence of such adhesions motion of the entire heart is mainly caused by respiration if there is no large pericardial effusion. We reduced this problem by predominantly studying end expiratory beats, in which there is little respiratory influence on motion of the entire heart.

In most patients with heart transplants there was a slow left ventricular relaxation pattern during follow up. In a subset of patients there was a tendency towards improvement of this pattern. Left ventricular hypertrophy caused by systemic hypertension, myocardial fibrosis, and persisting mild acute rejection are the most probable explanations for the slow left ventricular relaxation pattern. The total duration of ischaemic time of the donor heart was inversely related to the peak posterior wall thinning rate, and may have contributed to the slow left ventricular relaxation in patients with a long ischaemic time. Digitised left ventricular M mode echocardiography did not allow the non-invasive diagnosis of moderate acute rejection, either in a group or in an individual. This may be due to various haemodynamic factors that influence both wall thickness and cardiac function after cardiac transplantation.

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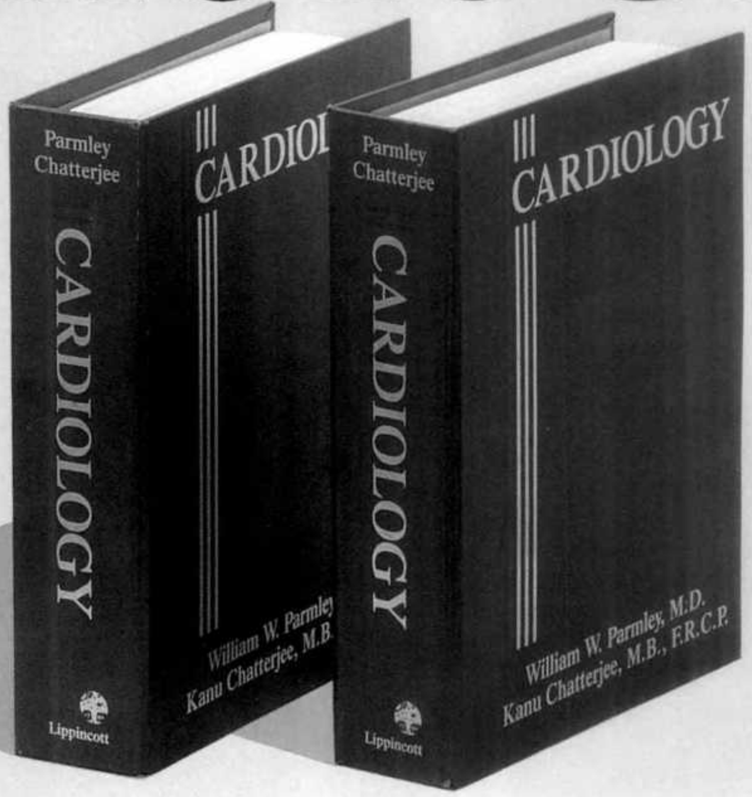

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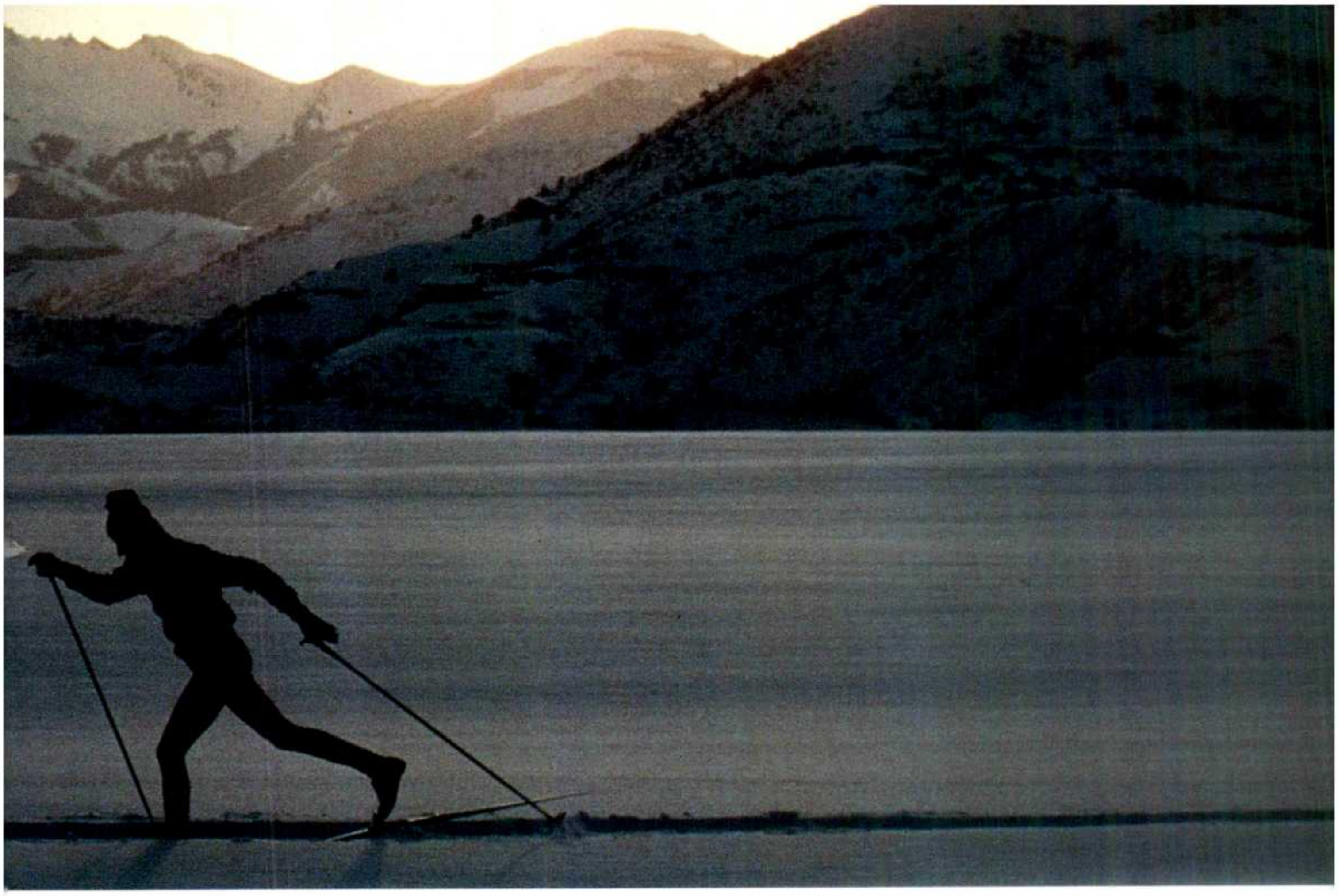

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PRESENTATION Manoplax tablets are available as white, irregular hexagonal film-coated tablets containing either 50mg or 100mg of flosequinan. The tablets are debossed on one side with either '50' or '100' and debossed with an identifying motif on the other. **USES** Manoplax is indicated for the treatment of chronic congestive heart failure and should be used together with diuretics and, where appropriate, with a cardiac glycoside, with or without ACE inhibitors. **DOSAGE AND ADMINISTRATION** The recommended dose of Manoplax is 100mg per day taken as a single dose in the morning, with or without food. The starting dose should be 50mg once daily for four weeks after which the dose should be increased to 100mg. A minority of patients may benefit from a dose of 150mg once daily. As symptomatic benefits may take four to twelve weeks to become fully apparent, an increase to this dosage should not be considered for at least twelve weeks and only after a full assessment of the benefit to the patient. A maximum daily dose of 150mg should not be exceeded. At this dose, the heart rate should be monitored and the dose reduced if excessive increases are observed. In clinical trials, no problem specific to the elderly has been observed; nevertheless, as with all drugs, the frail elderly patient with a particularly low bodyweight may respond to a lower dosage. In patients with severe renal (creatinine clearance <20 ml/min) or hepatic impairment, the dose of Manoplax should be maintained at 50mg once daily. Manoplax is not recommended for use in children as the safety and efficacy of flosequinan in this group have not been established. **CONTRA-INDICATIONS, WARNINGS, ETC. Contra-indications:** History of hypersensitivity to Manoplax. Manoplax should not be used where the patient's heart failure is associated with outflow obstruction. **Pregnancy:** There is no evidence on the safety of the drug in human pregnancy. If drug therapy is needed in pregnancy, this drug should be used only if there is no safer alternative. It is not yet known whether flosequinan is excreted in human milk, therefore caution should be exercised if Manoplax is administered to nursing mothers. **Precautions:** Manoplax should be given with caution and under supervision to patients with a systolic blood pressure below 90mm Hg; therapy should be instituted with a dose of 50mg. As with all vasodilating drugs, symptomatic hypotension can occur, particularly following initial dosing, although this has only rarely been observed with Manoplax. Nevertheless, patients should be cautioned about its possible occurrence. The dose should be reduced if excessive increases in heart rate are observed. **Side effects:** Following treatment with Manoplax, the adverse events reported are mostly consistent with the vasodilatory actions of the drug, namely: headache, dizziness, palpitations, tachycardia and symptomatic hypotension. The headache usually resolves on continuation of therapy and medically significant, exaggerated first-dose hypotension has rarely been observed. Gastrointestinal effects include nausea, vomiting and diarrhoea. Taste disturbance, due to the secretion of the drug in the saliva, has also been reported. Minor serum creatinine elevation is seen in some patients but is not associated with a raised blood urea nitrogen. **Drug interactions:** In clinical studies, some patients receiving Manoplax required reduction of their warfarin dosage. A formal interaction study revealed only minor changes in coagulation parameters; nevertheless, it is advisable to monitor the coagulation status of patients receiving anticoagulants and Manoplax concurrently. There are no significant changes in the kinetics of either Manoplax or digoxin when they are administered concomitantly. Caution should be exercised in patients receiving vasodilators, although in patients receiving ACE inhibitors or nitrates, the addition of Manoplax has been well tolerated. Cimetidine alters the pharmacokinetics of flosequinan consistent with its known effect on the cytochrome P-450 enzyme system. This is considered to be of little clinical significance. **PHARMACEUTICAL PRECAUTIONS** None. **LEGAL CATEGORY** POM. **PACKAGE QUANTITIES** Manoplax Tablets 100mg: Blister calendar pack containing 28 tablets. Manoplax Tablets 50mg: Bottle pack containing 30 tablets. Basic NHS price Manoplax Tablets: calendar pack of 28 x 100mg - £42.56. Manoplax Tablets: bottle of 30 x 50mg - £41.10. **PRODUCT LICENCE NUMBERS** Manoplax Tablets 100mg: 0014/0428, Manoplax Tablets 50mg: 0014/0443. **DATE OF PREPARATION OR LAST REVIEW** 22 July 1992. Further information is available from Boots Pharmaceuticals, a division of The Boots Company PLC, Nottingham.

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Fall in pulmonary vascular resistance in patients awaiting heart transplantation

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Abstract

***Background*—Raised pulmonary vascular resistance is associated with decreased survival after orthotopic heart transplantation and patients with this risk factor are usually denied transplantation. In a proportion of cases raised pulmonary vascular resistance may fall with time and medical treatment.**

***Methods*—Seven patients with high pulmonary vascular resistance (range 3·9–6·6 Wood units) at initial assessment for cardiac transplantation were restudied by right heart catheterisation after a period of seven to 17 months.**

***Results*—In five of the seven patients the pulmonary vascular resistance had fallen, allowing orthotopic heart transplantation to be performed in four. In one patient the resistance was static and in one it had risen. The mean fall in pulmonary vascular resistance for the group was (mean (SD)) 2·6 (2·7) Wood units, $p < 0·05$.**

***Conclusion*—Patients who have been denied transplantation on the basis of their raised pulmonary vascular resistance should be reassessed after four to six months if they remain otherwise clinically suitable.**

(*Br Heart J* 1992;68:365–8)

Patients with a raised pulmonary vascular resistance are generally regarded as unsuitable for orthotopic cardiac transplantation because of the high risk of perioperative death from right ventricular failure,[1 2] and reduced long-term survival.[3] It has recently been reported that a high pulmonary vascular resistance acutely unresponsive to intravenous vasodilators or high concentrations of inspired oxygen (so called fixed raised pulmonary vascular resistance) can fall with prolonged intensive medical treatment.[4]

Patients and methods

Seven patients clinically suitable for heart transplantation were studied. Six had coronary artery disease and one had dilated cardiomyopathy. All were men aged between 21 and 60.

Table 1 shows details of the patients and their medication. No patient had had an episode of myocardial infarction or cardiac decompensation less than five months before initial assessment. Only minor dose adjustments occurred during this time and the medication remained constant between the assessments.

The patients were assessed by right heart catheterisation on two occasions (table 2). The right heart was catheterised by either the brachial or femoral route with either a 7FG Swan Ganz thermodilution balloon catheter (Viggo Spectramed) or a 7FG multipurpose catheter (Cordis). Mean pulmonary artery and pulmonary capillary wedge pressure were measured electronically. Cardiac output was assessed either by thermodilution with a Spectramed cardiac output computer or by estimation of the oxygen uptake with a PK Morgan respiratory analyser and calculation from the arterial and pulmonary artery oxygen saturations by the Fick principle (table 2). When the thermodilution method was used an average from a minimum of three readings with an agreement of 5% or better was used.

Where the response to intravenous vasodilator was assessed, this was done by infusion of sodium nitroprusside in four cases and isosorbide dinitrate in one into a peripheral vein (table 2). Infusion was continued in increasing doses until a satisfactory decrease in pulmonary vascular resistance was noticed, or an arterial systolic blood pressure of 80 mm Hg was reached, or the patient became symptomatically hypotensive.

The difference in pulmonary vascular resistance between assessments was analysed by paired Student's t test.

Results

In five of the seven patients the pulmonary vascular resistance had decreased to less than 4 Wood units, and four have undergone standard orthotopic transplantation; one remains on the waiting list. In one patient the pulmonary vascular resistance had increased and in the other it had remained static. Table 2 shows details of the findings at right heart catheterisation. The mean resistance fell from 5·5 to 2·9; fall in resistance was mean (SD) 2·6 (2·7), $p < 0·05$.

Discussion

Orthotopic heart transplantation in patients with pulmonary hypertension is associated with an increased risk of perioperative death, principally from right heart failure early after operation.[1 2] It is also associated with reduced long-term survival.[3]

Pulmonary artery systolic pressure, trans-

Table 1 Patient details and total doses of drugs (mg/day)

Patient No:	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Age (y)	53	21	49	54	49	55	60
Aetiology	CAD	IDC	CAD	CAD	CAD	CAD	CAD
Medication:							
Captopril	—	37·5	37·5	—	37·5	37·5	75
Enalapril	5	—	—	10	—	—	—
Frusemide	80	160	120	80	80	160	40
Digoxin	0·125	0·25	—	—	—	—	0·25/0·125
Nitrate	80	—	120	—	—	40	—
Anticoagulant	Yes	Yes	No	No	No	No	Yes
Other			Xamoterol Amiodarone	Metolazone Aspirin Diazepam	Amiloride Xamoterol Cimetidine	Prochlorperazine Allopurinol	

CAD, coronary artery disease; IDC, idiopathic dilated cardiomyopathy.

pulmonary gradient (mean pulmonary artery pressure − mean pulmonary capillary wedge pressure), pulmonary vascular resistance (transpulmonary gradient/cardiac output) and pulmonary vascular resistance index (pulmonary vascular resistance × body surface area) have all been used to assess the suitability of patients for heart transplantation. No general agreement exists as to the most useful index.

Measurement of the pulmonary vascular resistance as an indication of the potential right ventricular load is theoretically attractive as it takes into account not only the pressure differences across the pulmonary vasculature but also the cardiac output at the time, and although this pressure flow relation, more correctly termed the pulmonary arterial resistance, is only a component of the impedance to right ventricular ejection, it has been shown to be the dominant factor especially when raised.[5] Some studies have suggested that pulmonary vascular resistance index, which takes into account body surface area, is a better predictive index of right ventricular failure after operation.[6] Others have suggested the reverse.[7] The appeal of these two measures is also their major weakness, however, as estimation of cardiac output may prove unreliable, and errors within the accuracy of the system make a substantial difference to the calculation of pulmonary vascular resistance. Thermodilution (the most convenient method), for example, is known to be inaccurate in the presence of tricuspid regirgitation,[8] an almost invariable accompaniment of severe congestive cardiac failure. Accordingly the transpulmonary gradient is used as the principal estimate of pulmonary resistance in many centres and there is evidence that it is as reliable as any other measure.[3, 9]

As well as the resting pressure and flow measurements it is possible to manipulate the vascular tone and cardiac output with drugs to examine the patients likely response to transplantation. Traditionally sodium nitroprusside has been used and evidence has suggested that a reversible or partially reversible resistance is predictive of a more favourable outcome than a fixed raised resistance.[6, 7] It has also been suggested that use of inotropes such as dobutamine or enoximone may be of value, the rationale being that these agents mimic the effect of transplantation by increasing cardiac output by an effect on contractility. Studies on the use of dobutamine and enoximone have suggested that mortality from right heart failure after operation can be improved by the use of exclusion criteria based on these methods.[10, 11]

A recent retrospective review of the Stanford data[7] has strongly supported the use of the pulmonary vascular resistance and its manipulation with nitroprusside as the best measurement (although no comparison with the use of inotropes was possible). The findings were that when patients with a resting pulmonary vascular resistance greater or less than 2·5 Wood units were compared, those with the higher pulmonary vascular resistance had a significantly increased postoperative mortality (nearly three times greater). Of these there was a further subdivision into three groups based on the response to nitroprusside: those in whom resistance fell to <2·5 Wood units but maintained a systolic blood pressure >85 mm Hg; those with resistance decreased to <2·5 Wood

Table 2 Indices of pulmonary haemodynamic function measured at right heart catheterisation in seven patients (1) initially and (2) at reinvestigation

	Case 1			*Case 2*		*Case 3*		
	1	*1+VD*	*2*	*1*	*2*	*1*	*1+VD*	*2*
INT			13		11			17
PA (M)	39	40	35	40	20	55	36	23
PCW (M)	22	19	30	20	10	36	18	18
CO	2·6	3·3	3·8	4·0	5·1	3·3	4·1	5·1
Method	O_2	O_2	TD	TD	O_2	TD	O_2	O_2
TPG	17	21	5	20	10	19	18	5
PVR	6·5	6·4	1·3	5·0	2·0	5·8	4·4	1·0
PVRI	11·7	11·5	2/3	13	5·2	11·6	8·8	2·0

+VD, after intravenous vasodilator (isosorbide dinitrate in case 1, sodium nitroprusside in cases 3, 4, 5, and 6); INT, interval in months between assessments; PA(M), mean pulmonary artery pressure (mm Hg); PCW(M), mean pulmonary capillary wedge pressure (mm Hg); CO, cardiac output (l/min); Method, method of measurement of cardiac output; O_2, measurement of oxygten uptake and calculation of CO from Fick principle; TD, thermodilution Swan Ganz catheter; TPG, transpulmonary gradient (mm Hg); PVR, pulmonary vascular resistance (Wood units); PVRI, pulmonary vascular resistance index (=PVR × body surface area, Wood units.m^2).

units at the expense of systolic hypotension (<85 mm Hg); and those whose resistance did not fall below 2·5 Wood units. Three month mortality in the three groups was 3·8%, 27·5%, and 40·6%. All of the deaths from right ventricular failure were in the second and third groups.

Our practice has been to measure the pulmonary vascular resistance and if it is raised to give intravenous sodium nitroprusside. We do not use rigid numerical limits although patients with a pulmonary vascular resistance of four to five Wood units or more are evaluated with nitroprusside. Others have published similar practices.[3]

In applying these guidelines it has been stressed that the risk, both immediately and long-term after heart transplantation, rises continuously with increaseing pulmonary resistance and that there is no sharp cut off point.[2 6]

A recent review advocated reassessment of patients awaiting orthotopic cardiac transplantation every four to six months to ensure that their pulmonary haemodynamics have not deteriorated but did not discuss the possibility of improvement.[12]

A study by Deeb *et al* compared the use of intravenous amrinone with conventional oral medication (diuretics, digoxin, and captopril) in potential heart transplant recipients with a raised pulmonary vascular resistance or transpulmonary gradient resistant to oxygen and nitroprusside.[4] A fall in resistance and transpulmonary gradient into an acceptable range for orthotopic transplantation was noted in most patients with both treatments (although intravenous amrinone was more effective than the oral regimen).

Our patients received treatment comparable with that of the conventional treatment group described by Deeb *et al*,[4] except that inpatient invasive monitoring was not performed and the doses of diuretic we used were smaller (360 mg frusemide daily plus metolazone in 10 out of 16 of their patients *v* 106 mg average dose of frusemide and metolazone in one out of six of our patients): doses of captopril were similar. The cases we describe had been stable for five to 12 months before initial assessment without further infarction or cardiac decompensation and their medication was stable during this period. No details are given of the pre-existing medication in their study, or of any temporal relation to an acute event. Thus it seems likely that our patients are most comparable with the subgroup of patients in that study's group 2 (conventional treatment) who failed to respond to treatment during the study period (six out of 16). This shows that even in this group of nonresponders improvement is possible over a more prolonged period.

From our findings and those already referred to it is clear that patients initially considered to be unsuitable for orthotopic heart transplantation due to unacceptable or marginally acceptable pulmonary haemodynamics, may improve either with intensive medical treatment or long-term conventional treatment. The possibility of such an improvement should be considered in any patient with a raised pulmonary vascular resistance that is thought likely to compromise a successful transplant.

We therefore recommend that patients who are in a stable condition and who are excluded from transplantation on the basis of their pulmonary vascular resistance should be reassessed after four to six months as their resistance may decline and allow successful transplantation.

We support the view that patients on the waiting list for heart transplantation should have pulmonary haemodynamic foundation reassessed every four to six months. They should also be reassessed in the event of a deterioration in their symptoms as the pulmonary vascular resistance may rise progressively even in the absence of a clearly defined cardiac event.

Addendum

The five patients whose pulmonary vascular resistance had fallen have now been transplanted. One of these was an emergency transplant in the setting of an acute deterioration and the patient died in the perioperative period. The other four were successful although two have died subsequently, one of rejection related to poor compliance with his immunosuppressive medication at four months after transplantation, and the other of a bowel lymphoma 15 months after transplantation. Of the two whose resistance did not fall one had died on the waiting list and the other is on the waiting list awaiting a suitable local donor.

Case 4			*Case 5*			*Case 6*			*Case 7*	
1	*1+VD*	*2*	*1*	*1+VD*	*2*	*1*	*2*	*2+VD*	*1*	*2*
		7			10			4		16
48	48	42	65	28	37	47	45	26	38	35
28	10	28	40	10	25	30	27	8	20	20
3·3	4·7	4·3	3·8	5·5	5·2	3·6	2·3	2·6	4·6	4·2
TD	TD	TD	O_2	O_2	TD	TD	O_2	O_2	O_2	TD
20	38	14	25	18	12	17	18	18	18	15
6·1	8·1	3·3	6·6	3·2	2·2	4·7	7·8	6·9	3·9	3·8
12·4	16·5	6·7	12·5	8·6	4·3	8·9	14·8	13·1	8·6	8·4

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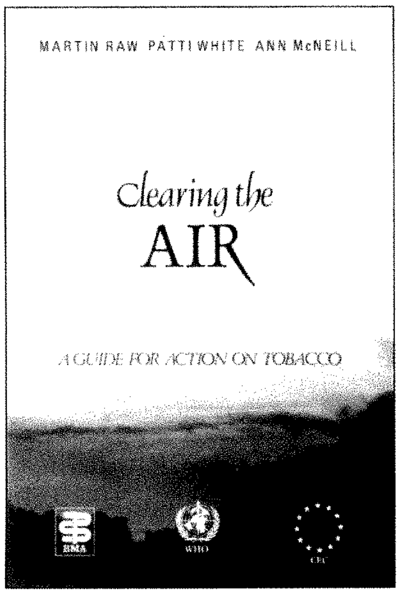
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Capoten Prescribing Information (abbreviated) CAPOTEN TABLETS **Presentation**: Tablets containing 12.5mg, 25mg or 50mg captopril. **Indication and Adult Dosage**: **Mild to moderate hypertension**: Capoten is indicated for first line treatment. The starting dose is 12.5mg bd. The usual maintenance dose is 25mg bd. This may be increased to 50mg bd. Treatment should be at the lowest effective dose. A thiazide diuretic may be added to Capoten if a satisfactory response has not been achieved. **Congestive heart failure**: Capoten is used together with diuretics, and where appropriate, digitalis, when diuretic therapy (such as frusemide 40-80mg or equivalent) is insufficient to control symptoms. Capoten must be started under close medical supervision. A starting dose of 6.25mg or 12.5mg may minimise any transient hypotensive effect. The usual maintenance dose is 25mg bd or tds. The usual maximum dose is 150mg daily. Delay dosage increases for at least 2 weeks, to determine if satisfactory response has occurred. A low initial dose is recommended in elderly patients who may have renal and other organ dysfunctions. **Contra-indications**: Hypersensitivity to captopril. Pregnancy and women of child bearing potential unless protected by adequate contraception. **Warnings/ Precautions**: Renal function should be assessed before and at appropriate intervals during therapy. Patients with renal impairment should not normally be treated with captopril. Do not use in patients with aortic stenosis or outflow tract obstruction. Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported but are rare in patients with normal renal function. Patients should report infections and Capoten withdrawn if neutropenia is suspected - See Data Sheet. Proteinuria is rare with prior normal renal function. Capoten should not be used routinely in patients with pre-existing impaired renal function, collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide. **Hypotension**: Symptomatic hypotension may occur occasionally with the f one or two doses, usually relieved by the patient lying down. Aggressive diuretic therapy may exaggerate hypotens responses usually within one hour of the initial dose of Capoten. Significantly reducing or discontinuing the diuretic dose 4-7 days prior to initiating Capoten may reduce the possibility of this occurrence. First dose hypotension does not preclu subsequent dose titration. Hypotension has been occasionally reported in patients on Capoten due to causes of acute volu depletion such as vomiting or diarrhoea. Renal artery stenosis, surgery/ anaesthesia, lactation, clinical chemistry - see D Sheet. **Serum Potassium**: Potassium sparing diuretics or potassium supplements should not be used routinely as ser potassium is usually maintained in patients on diuretics with Capoten. **Side Effects**: See Warnings. Rashes, angioedema, ta disturbance and gastrointestinal upset, usually mild and transient, have been reported. **Overdosage**: see Data Sheet. **Dr Interactions**: see Data Sheet. **Product Licence Numbers:** Capoten Tablets 12.5mg PL 0034/0221; Capoten Tablets 25mg PL 0034/0193; Capoten Tablets 50mg PL 0034/0194. **Basic NHS Price**: 12.5mg tablets 100 - £18.86; 25mg tablets 90 - £19.34; 50mg tablets 90 - £32.95. **Legal category**: POM. Capoten is a Squibb Trade Mark. Further information available on request from: Technical Services Department, E.R. Squibb & Sons Limited, B.M.S. House, 141-149 Staines Road, Hounslow, Middx. TW3 3JA. Telephone 081 572 7422. Date of preparation: Dec '90. **Reference:** 1. Cannon PJ et al, J Am Coll Cardiol 1983; 2: 755-763.

SQUIB

Early vasodilator treatment in myocardial infarction: appropriate for the majority or minority?

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Abstract

***Objective*—To assess the influence of vasodilator treatment started early after myocardial infarction on left ventricular size and function.**

***Setting*—Coronary care unit, Royal Infirmary, Edinburgh.**

***Patients*—105 patients with acute myocardial infarction (systolic blood pressure >90 mm Hg) were randomised within 24 hours of the start of pain. Unlike previous studies 88% of the patients received thrombolysis.**

***Methods*—Double blind randomised placebo controlled study with either 12·5 mg of captopril three times daily or 20 mg of isosorbide mononitrate three times daily for 28 days.**

***Main outcome measures*—Clinical outcome and left ventricular size and function assessed by echocardiography, radionuclide ventriculography, and magnetic resonance imaging.**

***Results*—There was no difference in left ventricular size or function in either treatment group as measured one week after the end of the trial. Even the placebo group tended to decrease left ventricular diameter over the four week study period (one week: 5·0 (0·1) *v*, five weeks: 4·8 (0·1) cm, NS). Four patients had an adverse clinical outcome in the placebo group whereas no adverse outcome was seen in the captopril group.**

***Conclusions*—Vasodilator treatment may be of limited value or of no benefit for most infarct patients, particularly those treated with thrombolytic agents. Captopril, however, may benefit patients at high risk.**

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In selected patients vasodilator treatment has been shown to prevent ventricular dilatation after infarction.[1-3] It is not known if this is true for all patients, particularly those treated with thrombolysis.

Thrombolytic treatment has beneficial effects on both the mortality[4,5] and residual left ventricular function[6,7] after myocardial infarction. Moreover thrombolysis reduces infarct size and the proportion of patients with persistent occlusion of the infarct related artery—the two factors recognised as the most important determinants of ventricular dilatation.[8,9] It seems likely that thrombolysis will modify the process of dilatation after infarction and therefore possibly the role of vasodilator treatment.

The aim of our study was to evaluate early vasodilator treatment in an unselected group of patients with acute myocardial infarction and therefore assess its role in the typical infarct patient.

As it is not clear which vasodilator might be most effective after acute myocardial infarction, two drugs were investigated in this double blind randomised study. The first was the angiotensin converting enzyme inhibitor, captopril, which has been shown to be beneficial in selected infarct patients[1-3] and also may reduce infarct size.[10] The second drug was isosorbide mononitrate, one of the nitrate vasodilators, which as a group have been reported to reduce mortality and ameliorate left ventricular dysfunction after infarction.[11,12]

Patients and methods

STUDY PROTOCOL

Patients admitted to the coronary care unit with suspected acute myocardial infarction were eligible for study, if they presented within 24 hours of the start of chest pain and the systolic blood pressure was >90 mm Hg. Previous myocardial infarction was noted. The study was approved by the local ethics committee and informed consent was obtained from all participating patients.

TRIAL TREATMENT

Patients (n = 105) were randomised to one of three treatments: placebo (n = 36), 20 mg isosorbide mononitrate (n = 33), or 12·5 mg captopril three times daily (n = 36). Captopril was initially given at a test dose of 6·25 mg and if this was well tolerated the full dose was given two hours later. If patients became hypotensive the protocol permitted omission of a dose or the use of half dose. Blood pressure was monitored every 15 minutes for the first two hours after the test dose. If the trial drug was tolerated, patients underwent treatment for 28 days. Patients who were withdrawn and stopped treatment before completing one week of the trial did not participate further in the study and therefore were not assessed for left ventricular size and function.

IMAGING

Left ventricular imaging was performed by three different techniques, so as to benefit from the strengths of each. Anatomical information was gained from echocardiography and nuclear magnetic imaging whereas cardiac function was assessed by radionuclide ventriculography. The main assessment of left ventricular size and function was performed at five weeks, one week after stopping drug treatment, as it is known that the pharmacological actions of vasodilators can influence these measurements. This protocol contrasts with the original work performed on captopril.[1 2]

ECHOCARDIOGRAPHY

Echocardiography was attempted in all patients at one and at five weeks after entry to the trial. Images were recorded on Hewlett-Packard echocardiography machines (both sonos 100 and 1000) with the patient lying semisupine in the semileft lateral position. Where the patient would comply the recordings were made at the end of expiration. Images were measured on the short parasternal axis at the level of the mitral valve tips. The anteroposterior and transverse diameters of the left ventricular cavity were measured at this level by the Hewlett-Packard calculation package. The results are given as the mean diameter.

RADIONUCLIDE VENTRICULOGRAPHY

Left ventricular ejection fraction was assesed by this radionuclide technique, five weeks after entry to the study. Patients were supine under a gamma camera (Siemens LEM) that was positioned in the modified left anterior oblique position with caudal tilt to provide good ventricular separation. The camera was interfaced to a Siemen's microdelta computer. The blood pool labelling was by injection of 700 MBq technetium-99m labelled human serum albumin (TCK2, CIS (UK) Ltd). After equilibration, an electrocardiogram gated acquisition of five million counts were made. The ejection fraction was calculated by a semi-automatic technique.[13]

MAGNETIC RESONANCE IMAGING

Patients were scanned roughly six weeks after the start of chest pain with a low field system (M and D Technology) operating at 0·08 tesla. A cardiac gating technique was used to synchronise acquisition of data during end diastole. Six or seven slices of 12 mm thickness and separation were required to obtain short axis views of the ventricular chambers from the cardiac apex to the outflow tracts. Two slices with a 32 ms time separation were obtained with each acquisition, which consisted of two averages of 128 frequency encoding steps and 64 phase encoding steps resulting in a pixel size of 3 × 6 mm. This data was interpolated to a 128 × 128 matrix (3 × 3 mm) and smoothed on the final display monitor for image analysis. A double spin echo pulse sequence was used with echo delay times of 42 and 120 ms for the first and second echos respectively. The repetition time was determined by the patient's heart rate but if this exceeded 95 beats/min data were only acquired every other heart beat.

Table 1 Baseline characteristics

	Placebo (n = 36)	*Isosorbide mononitrate (n = 33)*	*Captopril (n = 36)*
Sex (men:women)	31:5	30:3	30:6
Age (y)*	60·8 (8·4)	60·6 (11·2)	60·3 (9·4)
Site of infarction (anterior:inferior)	14:21	15:18	12:23
Previous infarction	4	4	0
Receiving thrombolysis	30	30	32
Time to thrombolysis (h)*	3·4 (1·7)	2·9 (0·9)	3·2 (1·9)
Time to trial treatment (h)*	13·6 (6·3)	15·3 (5·9)	14·4 (6·6)
Peak creatine kinase (U/l)*	1429 (1152)	1333 (975)	1494 (1178)
Completing trial treatment	27	29	31

*Continuous variables presented as mean (SD).

The first echo image routinely provided good anatomical detail with clear delineation of the endocardial border. To obtain the left ventricular volume an irregular region of interest was drawn around the endocardial surface on all slices by image analysis software. The value obtained were then summed and multiplied by the slice thickness to produce the total left ventricular volume.

STATISTICS

Comparison between groups was performed by Mann-Whitney U test for continuous variables and χ^2 test for the clinical outcome (Minitab release 6·1, Minitab, PA 16801, USA).

Results

BASELINE CHARACTERISTICS

The three groups were similar with respect to age, sex, site of infarct, and peak creatine kinase (table 1). The distribution of patients with previous myocardial infarcts was not even so these patients were not included in the assessment of clinical outcome and left ventricular size and function. One of the most striking characteristics of this study was that 88% of patients received thrombolysis with a mean time to thrombolysis of 3·2 hours. Most patients completed trial treatment.

REASONS FOR NOT COMPLETING TRIAL TREATMENT

Eighteen patients did not complete the trial (table 2). Five patients withdrew consent for trial participation shortly after entry into the study. One patient in the placebo group withdrew himself after 10 days because of breathlessness, later diagnosed as pulmonary oedema. A few patients were withdrawn for minor symptoms for example headache or indigestion. One patient developed glomerulonephritis which was attributed to streptokinase but despite this was withdrawn from the trial.

The more serious reasons for withdrawal included reinfarction (one patient on captopril) and prolonged hypotension with impaired tissue perfusion (three patients all on placebo). Four patients died within the first 28 days. In the placebo group one died shortly after randomisation and the other died from cardiac rupture at four days. Both patients that died in the isosorbide group had cardiogenic shock (one with a history of myocardial infarction).

ECHOCARDIOGRAPHY

Images were recorded from 89 out of the 105 patients. Image quality precluded quantitative

Table 2 Reasons for not completing trial treatment

	Placebo	*Isosorbide mononitrate*	*Captopril*
Consent withdrawn	2	1	3
Indigestion	1	—	—
Headache	—	1	1
Glomerulonephritis	1	—	—
Reinfarction	—	—	1
Hypotension with impaired perfusion	3	—	—
Died	2	2	—

No patient appears more than once in this table.

analysis in 17 (19% of those imaged). Ventricular dimensions were compared in the remaining patients with no evidence of previous infarction (n = 67).

There was no significant difference at one or five weeks in mean left ventricular diameter at either end systole or end diastole between the three treatment groups (fig 1). In no group was there a trend to dilatation and even patients in the placebo group tended to decrease left ventricular dimensions during the four weeks between studies (table 3).

RADIONUCLIDE VENTRICULOGRAPHY

Imaging was performed on 88 patients. Of these five were excluded from analysis because of previous infarction. The 17 patients that were not imaged had similar baseline characteristics to the remaining 88 patients except that they had a shorter duration of trial treatment due to withdrawal or death.

The left ventricular ejection fraction at five weeks was similar in the three groups (fig 2). The captopril group, however, had fewer patients with very low ejection fractions (<20%).

MAGNETIC RESONANCE IMAGING

Fifty six patients underwent magnetic resonance imaging, the number being limited by availability of the machine and periods when it was out of service. Four studies were discarded due to poor image quality and three abandoned due to claustrophobia. The remaining 49 patients had good quality images that were assessed.

Treatment with vasodilator made no significant difference to the five week end diastolic left ventricular volumes (fig 3).

CLINICAL OUTCOME

This is an important part of the assessment of the trial as patients who were withdrawn within the first week of the study do not appear in the data on ventricular size and function. Table 4 shows the distribution of patients with an adverse outcome. This analysis was based on an intention to treat and as a history of myocardial infarction would influence outcome, such patients have been excluded. Two men died and a further two men were withdrawn with cardiogenic shock in the placebo group. These last two patients had ejection fractions measured independently of this study and both were less than 20% (16% and 19%). Also there was one patient in the isosorbide group who died with cardiogenic shock. These patients missing from the left ventricular analysis are a potential source of bias and should be borne in mind when interpreting the results. It is of interest that no patient in the captopril group had such an adverse outcome. The difference in the clinical outcome between the captopril and placebo group was statistically significant (p < 0·05).

Table 3 Difference in mean left ventricular diameter between one and five weeks after infarction (cm)

	End diastole	*End systole*
Placebo	−0·25 (+0·15 to −0·65)	−0·05 (+0·60 to −0·50)
Isosorbide	−0·10 (+0·35 to −0·50)	−0·10 (+0·2 to −0·48)
Captopril	−0·25 (+0·15 to −0·55)	−0·15 (+0·15 to −0·50)

Differences and 95% CI calculated by Mann-Whitney U test.

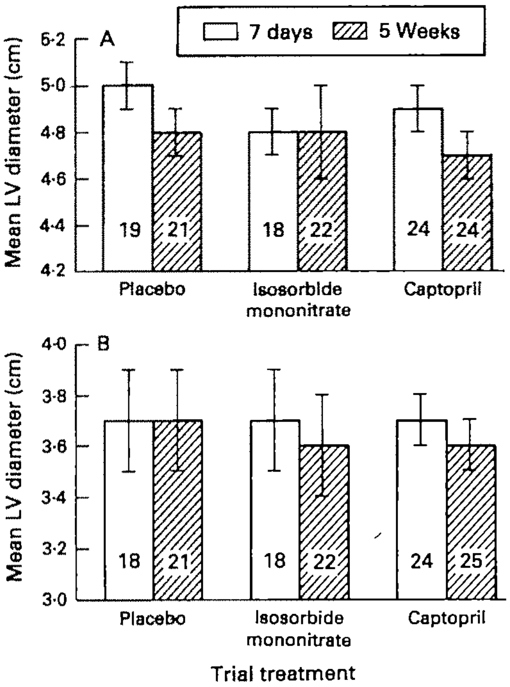

Figure 1 Echocardiographic measurement of mean left ventricular diameter; (A) end diastolic and (B) end systolic (mean (SEM); no of patients in boxes). There were no significant differences between groups.

Discussion

This study has shown no significant improvement in objective measures of left

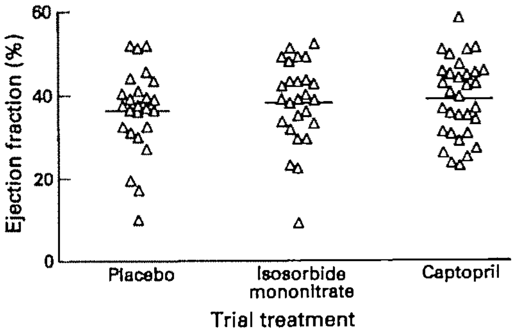

Figure 2 Left ventricular ejection fraction at five weeks calculated by radionuclide ventriculography. Each triangle represents one patient and the horizontal bars indicate the mean for each group. There were no significant differences between the groups. 95% CI placebo v isosorbide mononitrate, −6·5% to +3·0%; placebo v captopril, −7·0% to +3·5%; isosorbide mononitrate v captopril, −5·5% to +5·0%.

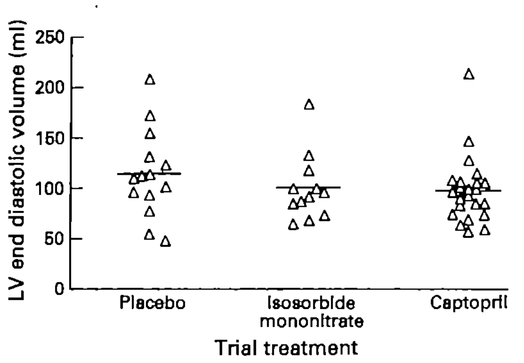

Figure 3 Scattergram showing left ventricular end diastolic volumes at five weeks measured by magnetic resonance imaging. A horizontal bar represents the mean ($n = 49$, NS). 95% CI placebo v isosorbide mononitrate, −15·9 ml to +33·2 ml; placebo v captopril, −11·2 ml to +28·6 ml; isosorbide mononitrate v captopril, −16·6 ml to +14·5 ml. There were no significant differences between the groups.

ventricular size and function from early vasodilator treatment. Captopril, however, may reduce the number of patients with an adverse clinical outcome. This result contrasts with other published studies reporting the beneficial effect of captopril[1–3] and nitrates[12] after infarction. In three of these studies no patient received thrombolysis[1,2,12] and in the fourth study patients treated with thrombolytic agents were included only if there was a Q wave infarction.[3] Also a two hospital study from Glasgow has recently reported that captopril treatment started within 24 hours of infarction significantly inhibited ventricular dilatation.[14] This study was of similar size to our own but once again this beneficial effect was seen in a population excluding those treated by thrombolysis.

Ventricular dilatation or remodelling has been extensively studied in patients with myocardial infarction not treated by thrombolysis. The proportion of infarcts that result in dilatation depends on the nature of the population studied. Previous work has shown that between 28% and 40% of patients with acute transmural myocardial infarction will undergo ventricular dilatation over the next six months.[8,15,16] The major risk factors for dilatation are transmural infarction, anterior infarction, extensive myocardial necrosis and persistent occlusion of the infarct related artery.[8] The particular importance of coronary artery patency in preventing dilatation has been shown in several studies. In one study failure to spontaneously reperfuse the infarct related artery proved to be a more important predictor of dilatation than infarct size.[9] Conversely, decreasing ventricular size after infarction was associated with a patent infarct related coronary artery. A second paper describes 78 patients with acute myocardial infarction, some of whom received thrombolysis. Left ventricular function was better in those patients with a patent artery either induced by thrombolysis or by spontaneous reperfusion.[17] Some of the larger trials of thrombolytic treatment have shown that patency of the infarct related artery is associated with lower long-term mortality.[18,19]

Table 4 Assessment of adverse outcome

	Placebo (n = 32)	*Isosorbide mononitrate (n = 29)*	*Captopril (n = 36)*
Died	2	1	—
Cardiogenic shock	2	—	—
Total	4	1	0

Placebo *v* captopril, $p < 0{\cdot}05$ (χ^2).
No patient appears more than once in this table. All patients with previous myocardial infarction have been excluded. Cardiogenic shock is defined as prolonged hypotension with impairment of perfusion of vital organs without evidence of right ventricular infarction.

Thrombolysis may have a beneficial effect on ventricular remodelling directly through myocardial salvage. In animal studies, however, late reperfusion without myocardial salvage has been shown to inhibit infarct zone expansion and result in thicker scar tissue.[20,21] This may explain why some studies, for example the second international study of the infarct survival (ISIS-2), have shown benefit of late thrombolytic treatment.[5]

In our study the placebo group showed no tendency to ventricular dilatation as the ventricular diameter tended to fall over the four week period. This contrasts with the outcome in the placebo groups of the studies by Sharpe *et al* and Pfeffer *et al.*[1,2] We believe that our study shows that in most patients receiving thrombolysis there is little tendency to remodelling and that vasodilator treatment does not produce major benefits in terms of ventricular size and function. Despite this, vasodilator drugs may have an important rôle in patients who are at increased risk of infarct expansion and dilatation. This is borne out from the adverse clinical outcome in our placebo group. Indeed even Pfeffer *et al* could only report a significant benefit from captopril treatment in those high risk patients with an occluded infarct related artery.[2]

Our study is small and therefore of limited statistical power. It does, however, show an important finding that should be considered in designing larger studies to assess the role of vasodilator treatment. All patients admitted to a coronary care unit may not benefit from this type of treatment: in particular, those at low risk of ventricular dilatation with small infarcts, inferior territory necrosis, and with patent infarct related coronary arteries.

We thank Ms F Taddei for technical assistance and Mrs V Campbell for secretarial skills. The drug treatment and patient randomisation was provided by the ISIS Office, Oxford, as part of the ISIS-4 pilot study and was funded by Bristol-Myers Squibb, who manufacture captopril (Captoten). Isosorbide mononitrate (Monit) was donated by Stuart Pharmaceuticals. The study was conducted, analysed, and interpreted independently of the companies.

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Evidence of increased platelet activation after thrombolysis in patients with acute myocardial infarction

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Abstract

***Objective*—To assess platelet activation after thrombolysis in patients with acute myocardial infarction.**

***Design*—Platelet function was assessed by measurement of the in vivo synthesis of thromboxane by gas chromatography-mass spectrometry of thromboxane's major urinary metabolite, 2,3-dinor-thromboxane-B_2.**

***Setting*—Coronary care unit of Huddinge University Hospital.**

***Subjects*—30 patients with acute myocardial infarction given either streptokinase 1·5 million units intravenously over one hour + 500 mg aspirin (n = 10), 500 mg aspirin (n = 10), or neither thrombolysis nor aspirin (n = 10).**

***Results*—Patients treated by thrombolysis had a 20-fold increase in thromboxane formation during thrombolysis compared with control patients not treated by thrombolysis (p = 0·0001). Until two days after thrombolysis thromboxane production in patients treated with streptokinase did not decrease to a value comparable with patients treated with aspirin but not given thrombolysis.**

***Conclusions*—Thromboxane production increased considerably during thrombolysis, possibly reflecting greatly enhanced platelet activation. The slow decrease in thromboxane formation after treatment with aspirin suggests that the efficacy of thrombolysis might be improved by more efficient antiplatelet treatment.**

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Platelet are activated in coronary thrombotic diseases such as acute myocardial infarction and unstable angina pectoris[1–3] and aspirin treatment was found to prevent myocardial infarction and deaths in patients with unstable angina and myocardial infarction.[4–6] Aspirin irreversibly acetylates the enzyme cyclo-oxygenase and thereby inhibits the synthesis of the potent platelet aggregator thromboxane A_2.[7] We found that aspirin was a very efficient inhibitor of thromboxane synthesis in patients with acute myocardial infarction.[8] These patient's however, were not treated with thrombolytic agents. The beneficial effect of thrombolysis on mortality[6 9] has made it the standard treatment for patients with myocardial infarction. The higher reinfarction rate in patients given streptokinase without aspirin[6 10 11] prompted us to study the effect of aspirin on the in vivo synthesis of thromboxane and prostacyclin in patients with acute myocardial infarction given thrombolysis.

Patients and methods

We studied 10 patients with acute myocardial infarction admitted to our coronary care unit within six hours of the onset of symptoms (3·3 (0·5) h (mean (SE)). The patients had not taken aspirin or any other cyclo-oxygenase inhibitor in the 10 days before the infarction and all gave their informed consent to the study. Regular medications were continued—that is, patients were given β-blockers if there was no contraindication, and glyceryl trinitrate and diuretics were given as necessary. All patients were given streptokinase (Behring, Marburg, Germany) (1·5 million units intravenously over one hour). Immediately after this the patients were given

Table 1 Data on 10 patients treated with streptokinase infusion (1·5 million units/60 min) within six hours after onset of symptoms of myocardial infarction (MI)

								Excretion during infusion of streptokinase (pg/mg creatinine)	
Case	*Age*	*Sex*	*Smoker*	*Previous MI*	*Duration of pain (h)*	*CK–MB peak (µkat/l)*	*Time to enzyme peak (h)*	*PGI_{2m}*	*TxA_{2m}*
1	69	F	—	—	6	6·1	12	353	709
2	59	F	Yes	—	4·5	6·5	18·5	592	4922
3	37	M	Yes	—	6	8·9	18·5	1340	29196
4	59	M	Yes	—	2	6·5	12·5	772	3266
5	72	M	—	Yes	1	4	10	675	2716
6	50	M	Yes	Yes	2	5·2	10	937	5534
7	73	F	—	Yes	3	5·4	25	140	1021
8	72	M	Yes	—	5	3·7	13	1522	2158
9	74	M	Yes	Yes	2·5	0·7	8·5	391	1492
10	80	M	—	—	2·5	1·1	17	908	90737
Mean (SEM)	64·5 (3·4)								

CK–MB, creatine phosphokinase isoenzyme MB. PGI_{2m}, prostacyclin metabolite; T × A_{2m}, thromboxane metabolite.

Table 2 Comparison of peak enzyme and protanoid concentrations (mean (SEM)) during myocardial infarction in patients given thrombolysis and aspirin (n = 10) with controls not given thrombolysis (but given aspirin (n = 10); and controls given neither (n = 10)

	Age (y)	*Sex (female (%))*	*Smokers (%)*	*CK–MB peak (μkat/l)*	*Peak (pg/ml creatinine)*	
					PGI₂m	*TxA₂m*
SK + aspirin	64·5 (3·4)	30%	60%	4·8 (0·7)	1187 (449)	11966 (7514)
Aspirin	60·7 (3·5)	20%	40%	3·2 (0·6)	1078 (491)	522 (137)
Controls	63·9 (2·1)	10%	30%	3·1 (0·6)	755 (268)	650 (145)

SK, streptokinase; CK–MB, creatine kinase isoenzyme MB; PGI_2m, prostacyclin metabolite; T × A_2m, thromboxane metabolite.

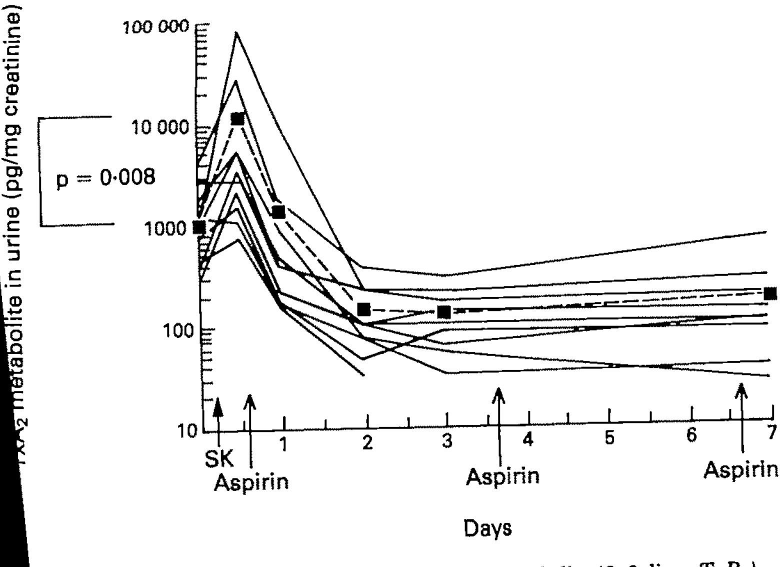
aspirin (500 mg) in buffered water solution (Bamyl-S, Hassle, Sweden) and this treatment was repeated every third day. Urine was collected before treatment, soon after thrombolysis, and then as 24 hour collections for days 1, 2, 3, and 7.

Table 1 gives data on the individual patients. As controls we used 20 patients with myocardial infarction who were not given thrombolysis. Those patients were recruited before thrombolysis and aspirin became the routine treatment at our coronary care unit. They had no contraindications to the use of aspirin and in all respects resembled the thrombolysis patients. Ten of the controls were given neither aspirin nor streptokinase and 10 were given aspirin in the same protocol as the patients treated with thrombolysis.

Otherwise all 30 patients were treated in an identical way—that is, were given β-blockers if there was no contraindication, and glyceryl and diuretics were given when necessary. Patient characteristics were matched. Acute myocardial infarction was diagnosed by the WHO criteria. The study was approved by the ethics committee at Huddinge University Hospital.

ANALYSIS

Urinary 2,3-dinor-TxB_2 and 2,3-dinor-6-keto-$PGF_{1\alpha}$ were analysed by gas chromatography-mass spectromety, with tetra-deuterated carriers and internal standards.[12 13]



ure 1 Urinary excretion of a thromboxane (TxA_2) metabolite (2, 3 dinor-TxB_2) 10 patients treated with infusion of streptokinase (SK) followed by an intermittent e of aspirin (500 mg each third day). Mean is shown by a broken line.

STATISTICAL METHODS

Results are given as mean (SE) and analysed by analysis of variance. Because thromboxane values after thrombolysis were not normally distributed the data were logarithmically transformed before analysis.

Results

All patients had a transmural infarction. Baseline characteristics and infarction variables such as peak enzyme concentrations, age, sex, and previous treatment with β blockers were similar for patients given thrombolysis and for control patients (table 2). Infusion of streptokinase increased the initial thromboxane metabolite concentration 10-fold (fig 1) and the peak concentration was approximately 20 times higher than in the two control groups (fig 2; p = 0·0001).

As figs 1 and 2 show, thromboxane production fell after the first dose of 500 mg aspirin, but only to a concentraton similar to that found in control patients not treated with aspirin or thrombolysis. On the second day after thrombolysis thromboxane production had fallen to the same concentration as measured in the patients treated with aspirin but not thrombolysis (fig 2). Peak prostacyclin concentrations were increased to a similar extent in all groups (table 2).

One patient in the thrombolysis group died of severe congestive heart failure on the third day. There were no reinfarctions within a 30 day period. Furthermore, no side effects of aspirin were reported. Glyceryl trinitrate consumption was similar in the three groups.

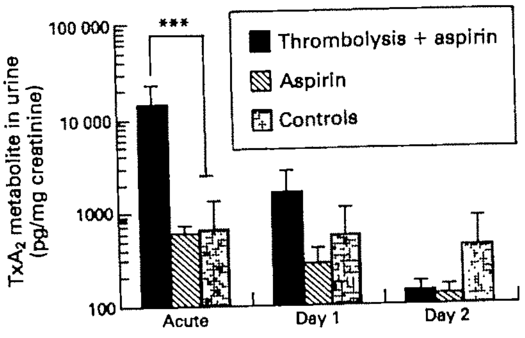


*Figure 2 Urinary excretion of a thromboxane (TxA_2) metabolite (2, 3-dinor-TxB_2) in patients with an acute myocardial infarction treated with streptokinase (SK) and aspirin: thrombolysis + aspirin (n = 10); only aspirin (n = 10), or neither (n = 10). Values are mean (SEM). ***p < 0·001.*

Discussion

We found a 20-fold increase in thromboxane formation when patients with acute myocardial infarction were treated with thrombolysis. The most obvious explanation for this finding was that platelet activation was increased during thrombolysis. Fitzgerald *et al* reported a similar tendency for thromboxane production to increase during thrombolysis in two patients.[14]

Patients given thrombolysis without antiplatelet therapy are reported to have an increased reinfarction rate,[6 10 11] probably reflecting reocclusion of previously opened coronary arteries. Furthermore, repeated angiography has shown evidence of early reocclusion.[15] In a study reported by Six *et al* there was evidence suggesting that the higher the dose of streptokinase the higher the initial patency rate but also the higher the reinfarction rate.[16]

Our findings accord with the suggestion that the increase in reinfarction rate is caused by greatly enhanced platelet activation/instability (as shown by the increase in thromboxane formation). In the ISIS-2 study the addition of aspirin to streptokinase reduced mortality even further.[6] The dose of aspirin given in ISIS-2 was only about a quarter of the dose we gave. Despite the higher dose of aspirin in our study it was not until day 2 that thromboxane production fell to values found in patients with acute myocardial infarction who were treated with aspirin but not thrombolysis. These results indicate that the efficacy of thrombolysis could be improved if patients were also given more effective antiplatelet therapy. Perhaps the initial high patency rate could be better preserved if aspirin were given before thrombolysis or if a thromboxane receptor antagonist were given with a cyclo-oxygenase inhibitor or thromboxane synthase inhibitor.[17] Our results may help to explain why treatment with low dose aspirin (80 mg) in conjunction with thrombolysis was relatively ineffective.[18]

We found that thromboxane formation increased 20-fold when patients with acute myocardial infarction were given streptokinase. This increase probably reflects a considerable platelet activation. Our results strongly suggest that the combination of thrombolysis with efficient antiplatelet therapy would improve results in patients with myocardial infarction, especially when thromboxane receptor antagonists become available.

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Left atrial and left ventricular diastolic function during acute myocardial ischaemia

J T Stewart, M Grbic, U Sigwart

Abstract

***Objective*—To study indices of diastolic left ventricular function during the first few seconds of myocardial ischaemia.**

***Design*—Isovolumic and total relaxation times and left atrial and left ventricular dP/dt were identified from high fidelity (micromanometer) pressure recordings in the left ventricle and left atrium during percutaneous transluminal angioplasty of the left anterior descending coronary artery.**

***Patients*—20 patients with isolated disease of the left anterior descending artery and normal left ventricular function.**

***Results*—The isovolumic relaxation time lengthened during the first seven to nine seconds of ischaemia; then it shortened by an average of 15% up to the twentieth second, initially as a result of increased left atrial contractility and subsequently because of impaired ventricular relaxation. Ventricular ischaemia resulted in impaired left ventricular diastolic compliance, as shown by an increase in the total relaxation time, before there was evidence of systolic impairment. Minimum dP/dt decreased progressively (by −37% at the twentieth second of ischaemia), whereas maximum dP/dt fell only after 20 seconds of ischaemia (by −11%).**

***Conclusions*—Relaxation and filling of the left ventricle (indices of diastolic function) are more sensitive to myocardial ischaemia than myocardial contractility and systolic function. Left atrial contractility increases during left ventricular ischaemia.**

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The physiology of left ventricular diastole is complex and the determinants of left ventricular filling are poorly understood. In the absence of aortic regurgitation or a defect of the interventricular septum, left ventricular filling begins at the onset of mitral valve opening and ends with mitral valve closure. Diastolic transmitral blood flow is determined by the interrelation of active left ventricular relaxation, chamber compliance, atrial contraction, and venous return from the pulmonary circulation. A tripartite mechanism of normal left ventricular filling has been described: a rapid filling phase that begins immediately after mitral valve opening and lasts about 200 ms, followed by a period of slow filling or diastasis, the duration of which is dependent on the heart rate. Left ventricular filling during sinus rhythm finishes with left atrial contraction.[1 2]

Although myocardial ischaemia is known to increase the left ventricular filling pressure (left ventricular end diastolic pressure) its effect on this tripartite mechanism has not been well characterised and in humans cannot be studied in the setting of myocardial infarction or spontaneously occurring angina pectoris. In an earlier paper we described the use of controlled myocardial ischaemia of the anterior left ventricular wall during angioplasty of the left anterior descending coronary artery (LAD) to study the effects of ischaemia on left atrial function.[3] In this study we used the same model to investigate the effect of segmental left ventricular ischaemia on the separate determinants of left ventricular filling (active relaxation, chamber stiffness, and left atrial contraction).

Patients and methods

PATIENTS

We studied 20 patients (16 men and four women) aged 40–71 (mean 49) years during elective coronary angioplasty. All patients had stable angina pectoris of effort and were in sinus rhythm. Diagnostic coronary arteriography had shown significant disease of the proximal left anterior descending artery (LAD) with a reduction of luminal diameter of ≥75% (estimated by the operator) and no other significant coronary disease. Patients with a collateral supply to the LAD territory were excluded from the study. All patients had normal left ventricular function at rest, and none had disease of either the aortic or mitral valves. None had a defect of the interventricular septum.

The procedure was approved by the hospital ethics committee and written informed consent was obtained in advance from each patient. All patients were given premedication with diazepam (10 mg), nifedipine (10 mg), and aspirin (500 mg). Routine antianginal agents were stopped at least 24 hours before the angioplasty was performed.

Methods

We used the femoral approach for cardiac catheterisation. A double micromanometer catheter with 5 cm between the sensors (Millar PC 771) was introduced into the left

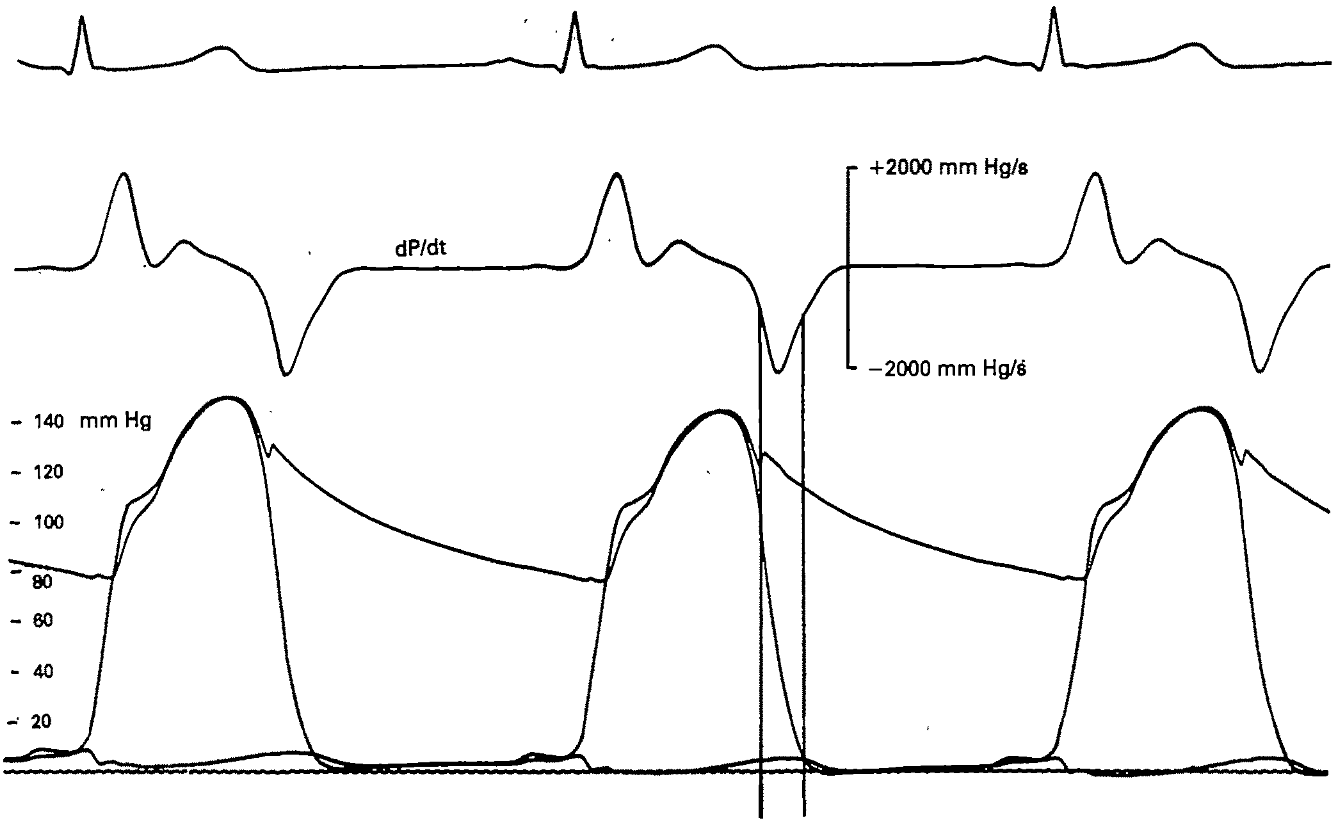


Figure 1 Simultaneous recordings of the electrocardiogram; left ventricular dP/dt; and micromanometer aortic, left ventricular, and left atrial pressures. The notch on the left atrial trace coincided with aortic valve closure; the parallel vertical lines indicate the isovolumic relaxation time (interval from aortic valve closure to the crossover of left ventricular and left atrial pressures).

heart by the transseptal route; the distal pressure sensor was located in the left ventricle and the proximal sensor in the left atrium. All patients were given intravenous heparin (10 000 units) once transseptal puncture had been performed. An 8F left coronary artery guiding catheter was positioned from the right femoral artery. In five patients a 7F pigtail catheter was inserted retrogradely into the left ventricle from the left femoral artery.

The micromanometers were calibrated electronically against a mercury manometer before insertion. Simultaneous recordings of left ventricular and left atrial pressure and the first order derivatives with respect to time (dP/dt) of left ventricular pressure were made on photographic paper and on digital tape. Left atrial and left ventricular pressures were monitored continuously during LAD angioplasty, which was performed with a conventional co-axial dilatation system. Balloon inflation was maintained for 20–30 seconds and repeated up to five times until a satisfactory angiographic result had been obtained. In five patients, bi-plane left ventricular angiography was performed before angioplasty and during the first 5–10 seconds of balloon inflation.

The duration of the isovolumic relaxation time (the interval from aortic valve closure to mitral valve opening) was used as an index of active left ventricular relaxation. As has been shown previously, it is possible to identify aortic valve closure from a vibration on the high fidelity left atrial pressure trace, which coincides with the dicrotic notch in the aortic pressure trace.[3] The isovolumic relaxation time was measured from simultaneously recorded high fidelity traces of the left ventricular and left atrial pressures as the interval from the vibration of aortic valve closure in the left atrial trace to the crossover of the left ventricular–left atrial pressure tracings. "Total relaxation time" was calculated from aortic valve closure to the nadir of the left ventricular pressure curve during diastole (fig 1).

Assessment of a change in left ventricular stiffness arising from acute ischaemia was made by analysis of regional left ventricular wall motion, before and during balloon inflation in the LAD. Left atrial function before and during acute ventricular ischaemia was assessed by analysis of the left atrial pressure trace.

Changes from control values were assessed by a paired *t* test (5% level of significance).

Results

The table lists the haemodynamic indices as means (SD). The heart rate increased slightly during balloon inflation from the control value of 72 (6) beats/min; the increase was statistically significant by the twentieth second of inflation (77 (9) beats/min ($p < 0.05$)). Left ventricular systolic pressure did not change during the first seven seconds of ischaemia, but had declined by 11% at the end of 14 seconds from 149 (12) mm Hg to 132 (14) mm Hg ($p < 0.05$). At the end of 20 seconds it had fallen

Table Effects of balloon occlusion on haemodynamic function

			Balloon occlusion							
	Control		*7 s*		*14 s*		*20 s*		*Recovery*	
HR	72	(6)	73	(7)	76	(10)	77	(9)*	73	(7)
LVSP (mm Hg)	149	(12)	147	(11)	132	(14)*	125	(9)*	149	(9)
LVEDP (mm Hg)	17	(6)	19	(7)	23	(4)*	29	(7)*	18	(7)
LA "a" (mm Hg)	23	(5)	25	(6)	32	(8)*	41	(3)*	22	(5)
LA "v" (mm Hg)	25	(6)	29	(7)*	39	(5)*	49	(4)*	25	(7)
IVR (ms)	82	(7)	93	(6)*	74	(7)*	70	(4)*	83	(8)
TRT (ms)	130	(9)	145	(8)*	>		>		131	(12)
LV dP/dt_{max} (mm Hg/s)	1453	(219)	1449	(221)	1381	(232)	1299	(229)*	1450	(250)
LV dP/dt_{min} (mm Hg/s)	1570	(230)	1370	(241)*	1197	(230)*	991	(187)*	1610	(240)

*$p < 0.05$ compared with control value (paired *t* test).
>, greater than previous value, but impossible to measure accurately.
HR, heart rate (beats/min); LVSP, LVEDP, left ventricular systolic and end diastolic pressure respectively; LA "a", LA "v" = "a" and "v" waves in the left atrial pressure trace; IVR, isovolumic relaxation interval; TRT, total relaxation time.

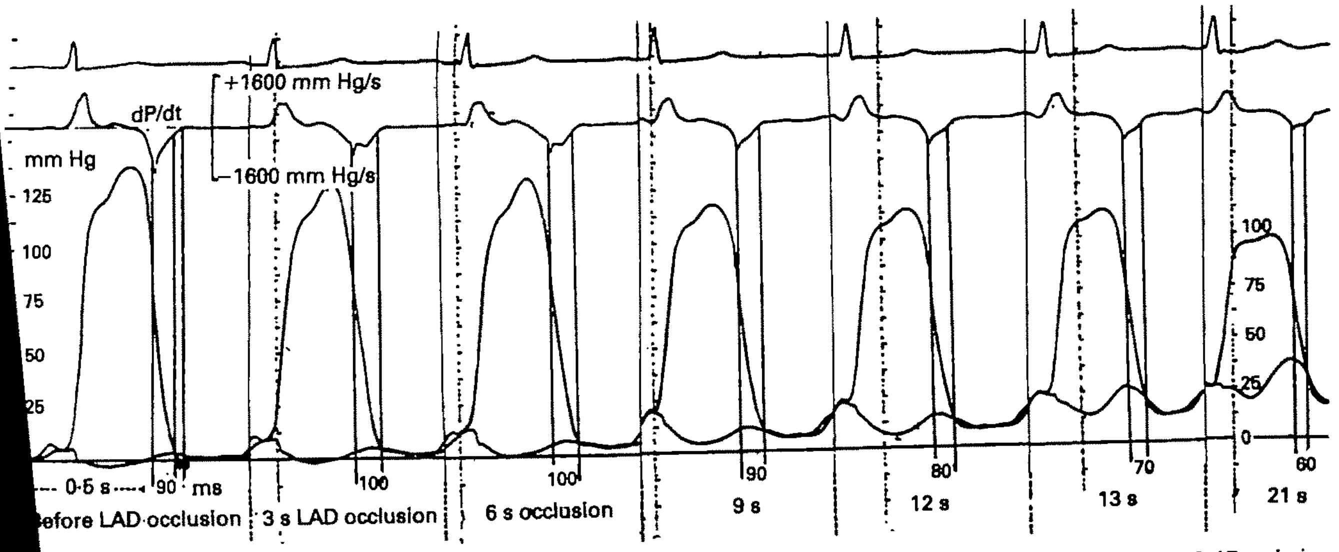
by 16% to 125 (9) mm Hg ($p < 0.05$). Left ventricular end diastolic pressure rose during inflation from 17 (6) mm Hg at baseline to 23 (4) mm Hg after 14 seconds ($p < 0.05$) and to 29 (7) mm Hg after 20 seconds ($p < 0.05$).

At baseline before inflation left ventricular isovolumic relaxation time was 82 (7) ms and peak negative dP/dt (dP/dt_{min}) was 1570 (230) mm Hg/s. Within two to three seconds of LAD occlusion dP/dt_{min} decreased and after five seconds there was deformation of the ascending limb of negative dP/dt. After seven seconds of LAD occlusion the isovolumic relaxation time had lengthened to 93 (6) ms ($p < 0.05$) and dP/dt_{min} had decreased to 1370 (241) mm Hg/s ($p < 0.05$). After nine to 10 seconds of LAD occlusion the isovolumic relaxation time began to shorten again and with periods of ischaemia of 15 to 20 seconds duration it fell to 70 (4) ms (fig 2).

Total left ventricular relaxation time began to lengthen after three seconds of LAD occlusion; 5–6 seconds after occlusion the nadir of the diastolic pressure curve had moved into later diastole producing a diastolic pressure wave that resembled a hammock (fig 2). This pattern of abnormality persisted until the end of LAD occlusion, but with increasing duration of ischaemia it became increasingly difficult to measure total left ventricular relaxation time accurately.

Within the first five seconds of LAD occlusion there was asynchronous motion of the anteroapicoseptal wall of the left ventricle, with late systolic shortening occurring during the period of isovolumic relaxation. This late inward movement during the rapid filling period of the left ventricular coincided with the notch on the ascending limb of the negative dP/dt signal and may contribute to the impedance to left ventricular filling. There was no rise in left ventricular filling pressure at this point, but the diastolic pressure curve took the hammock-like form described earlier.

Mean left atrial pressure rose within the first seven seconds of LAD occlusion from 13 (5) to 18 (6) mm Hg. The amplitude of the "a" and "v" waves increased from 23 (5) and 25 (6) mm Hg respectively to 25 (6) and 29 (7) mm Hg after seven seconds. After 14 seconds of occlusion the amplitude of the "a" and "v" waves had increased to 32 (8) and 39 (5) mm Hg ($p < 0.05$), and after 20 seconds had increased further to 41 (3) and 49 (4) mm Hg ($p < 0.05$) (fig 3). The greater increase in the "v" wave over the "a" wave was responsible for the significant shortening of isovolumic relaxation time. Maximum left atrial dP/dt rose from 220



re 2 *Simultaneous recordings of the electrocardiogram, left ventricular dP/dt and left ventricular and left atrial pressure during LAD occlusion. isovolumic relaxation time lengthened initially and then shortened as the duration of ischaemia increased (see text). The increase in total ation time produced a hammock-like appearance in the diastolic left ventricular pressure trace.*

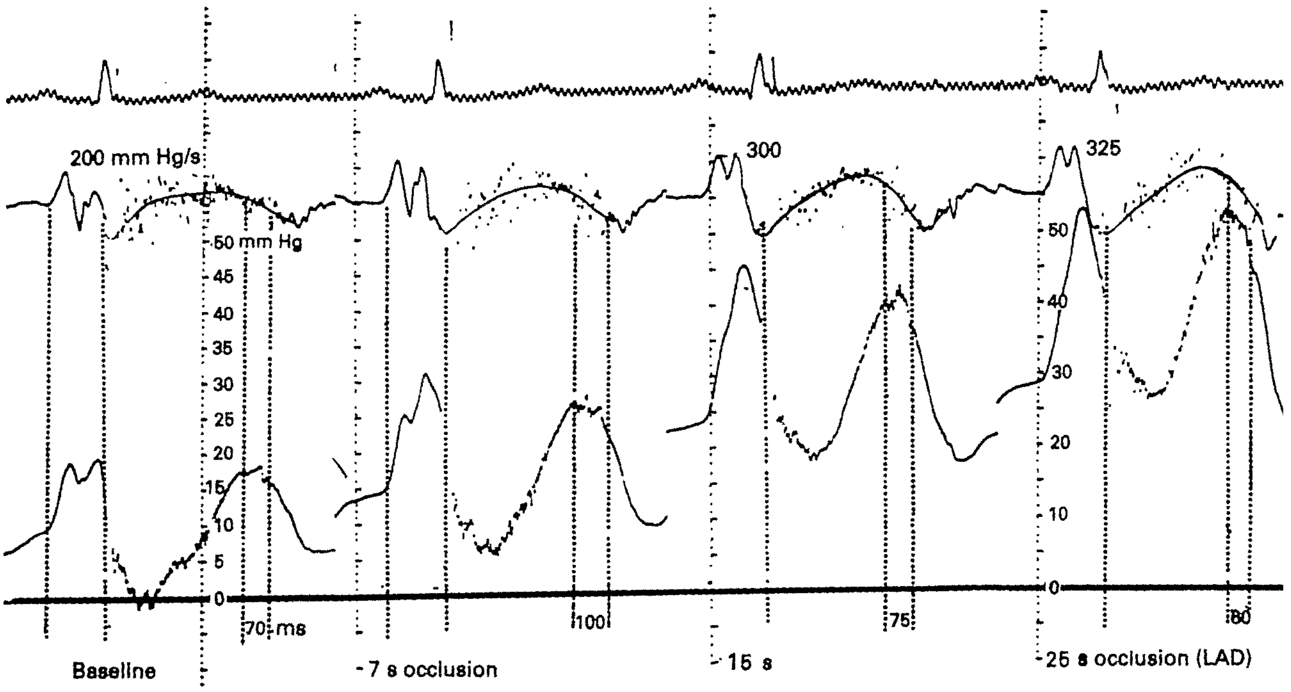


Figure 3 Simultaneous recordings of the electrocardiogram, left atrial dP/dt, and left atrial pressure during LAD occlusion. The greater increa the "v" wave over the "a" wave was responsible for the earlier crossover of left atrial and left ventricular pressures and the shortening of the isovolumic relaxation time. Atrial dP/dt increased with prolonged ischaemia.

(40) to 350 (20) mm Hg/s during ventricular ischaemia, suggesting increased left atrial contractility.

Ischaemia of the anterior left ventricular wall also affected the systolic function of the ventricle, but later and to a lesser degree. Peak positive dP/dt (dP/dt_{max}) fell slightly throughout the period of balloon inflation from the control value of 1299 (229) mm Hg/s, but the decline did not reach statistical significance until the twentieth second of ischaemia (1299 (229) mm Hg/s, $(p < 0{\cdot}05)$.

Discussion

In the normal heart, left ventricular filling immediately after mitral valve opening is rapid, with a peak transmitral flow rate of 500 ml/s (higher than the rate of flow across the aortic valve during left ventricular ejection). This phase of rapid filling in early diastole lasts about 200 ms and is followed by a phase of slower volume increase (diastasis), the duration of which is dependent on heart rate. The final phase of ventricular filling occurs with atrial systole. Myocardial relaxation, by which the myocardium returns to its original or presystolic (end diastolic) length and tension, is a complex, energy dependent process[4] which may be the major determinant of the early diastolic filling.[5] Brutsaert *et al* suggested that it is subject to a triple control mechanism: deactivation, loading, and non-uniformity of load and inactivation in time and space.[1 2]

The rate of left ventricular relaxation is principally determined by two indices—the maximal rate of left ventricular pressure fall during isovolumic relaxation (dP/dt_{min}) and the time constant of the fall in left ventricular pressure during isovolumic relaxation (T),[6–10]—but exact measurement of myoc relaxation is difficult. The peak negative is influenced by heart rate, systolic pres end systolic volume, and other factors.[7] time constant of the left ventricular pre fall during isovolumic relaxation relatively independent of other determina cardiac performance, but is a simple m matical approximation of the pressure de a monoexponential function whereas the sure decay is more complex. The isovo fall in left ventricular diastolic pressure d the first 20 seconds of coronary occlusion a monoexponential function,[11] thus its constant is of limited usefulness in the stu diastolic function in animals[11] or in huma

Nevertheless, assessment of myoc relaxation is of theoretical importance i study of acute ischaemia, and mech coronary occlusion at the time of cor angioplasty provides an ideal model. Be there seems to be no single measuremen described that provides an adequate ind the relaxation process in ventricular my dium, we used the direct determination duration of isovolumic relaxation and the relaxation time for this purpose. This volumic relaxation interval represents the taken for left ventricular pressure to drop the level of aortic diastole to that of th atrium, and is affected by the time cour relaxation as well as by the magnitude o pressure drop. Relaxation continues mitral valve opening until the nadir of th ventricular diastolic pressure, thus total rel tion time is the isovolumic relaxation int plus the time from mitral valve opening t lowest point of the left ventricular dias pressure curve.

Left ventricular chamber stiffness is a f conditioning was not carried out, and sleep stage and chest wall movements were not assessed. In no case was oxygen treatment required during the recording period.

ELECTROCARDIOGRAPHIC MONITORING

Conventional long-term electrocardiographic tape recording techniques were performed with an Oxford Medilog 4000-II recording and analysis system. Recordings were analysed for frequency of extrasystoles and modified Lown grade. Frequency of extrasystoles was divided into three bands: $\leqslant 10$, >10 $\leqslant 30$, and >30 extrasystoles in any hour. The Lown grade was dichotomised between those with Lown grade III or more (multiform, couplets, or non-sustained ventricular tachycardia) and those with Lown grade I or II (uniform and non-repetitive forms). In all cases, the electrocardiographic recording period and the oximetry recording period were the same.

MEASUREMENT OF EJECTION FRACTION

Ejection fraction was estimated by conventional techniques, with either cineventriculography (Dodge RAO method) in patients undergoing cardiac catheterisation (n = 21), and gated blood pool scanning (n = 10), or cross sectional echocardiography (n = 3) in those not undergoing catheterisation.

CLINICAL ASSESSMENT

All patients underwent a full clinical assessment, including a full history and physical examination, 12 lead electrocardiography and chest radiography. Drug treatment was continued unchanged; the treatment at the time of study was recorded. No patients were taking anti-arrhythmic agents.

STATISTICS

Continuous variables are expressed as mean (SD) and were compared by two tailed t test. Discrete variables were compared by the χ^2 test with Yates's continuity correction.

Results

PATIENTS STUDIED

A total of 37 patients were studied; in three cases, data were incomplete, leaving a study group with complete data comprising 34 patients. Of the incomplete cases, in two the Holter recording was destroyed due to a fault with the tape transport mechanism; one patient was excluded because of an inadequate oximetry recording. Good oximetry recordings proved feasible in patients with poor left ventricular function. The mean age of the study group was 60·5 (median 62, range 27–80) years and 2/34 (6%) were women. In most (29/34, 85%) the aetiology of the left ventricular disease was ischaemic; three (9%) had dilated cardiomyopathy, one had valvar heart disease, and one had both valve and coronary disease. All were in NYHA classification grades II-IV for dyspnoea; nine grade IV, 12 grade III and 13 grade II. All were receiving treatment with diuretics and most were also receiving treatment with an angiotensin converting enzyme inhibitor. No patients were taking anti-arrhythmic agents.

OXIMETRY

The mean (SD) saturation during the recording period was 93 (3)%, median 94%, range 84–97%; four patients (12%) had a mean saturation below 90%.

Oximetry tracings were classified into three types: a recording without episodic hypoxia, when there was little fluctuation in oxygen saturation, with no dips below 90%; sinusoidal fluctuations in oxygen saturation confirmed visually to correspond to Cheyne-Stokes respiration, with dips below 90% saturation; and other patterns where dips in oxygen saturation below 90% occurred (fig 1). A total of 14/34 (41%) showed no abnormality of oxygen saturation profile; 13/34 (38%) showed the Cheyne-Stokes pattern, and 7/34 (21%) had other patterns. The dip frequency ranged from 0·1 dips/h to 20/h; 6/34 (18%) had a dip frequency of >10/h. The mean dip frequency was 4·8 (median 2·7) dips/h. Dip frequency was 7·3 (6·6) dips/h in those with NHYA class IV dyspnoea, compared with 5·1 (5·8) dips/h in those with class III dyspnoea (NS).

ELECTROCARDIOGRAPHIC MONITORING

A total of 20/34 (59%) of patients had a frequency of extrasystoles of $\leqslant 10$/h; 10/34 (29%) >10 and $\leqslant 30$/h; four had >30/h. Lown grade IVB arrhythmias (non-sustained ventricular tachycardia) were seen in 11/34 (32%); IVA arrhythmias (couplets) were seen in 8/34 (23%) and Lown grade $<$III arrhythmias in 14/34 (41%). One patient had grade III arrhythmias (multifocal extrasystoles alone).

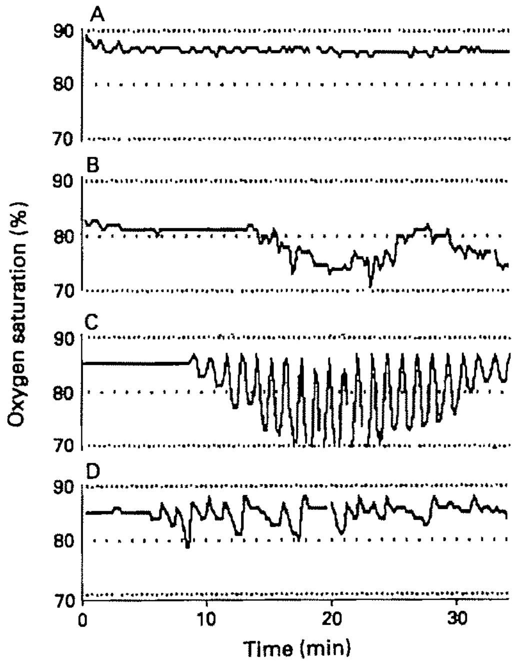


Figure 1 Patterns of oxygen saturation dips. (A) little fluctuation in saturation level, no dips below 90%; (C) sinusoidal pattern due to Cheyne-Stokes respiration; (B, D) other patterns.

Relation between arrhythmias and results of oximetry

	Lown >III	*Lown <III*	*p Value*
Ejection fraction (mean (SD)%)	25 (12)	27 (14)	NS
Dip frequency (mean (SD)/h	6·7 (5·5)	2·2 (3·4)	<0·01
Mean (SD) saturation (%)	92·3 (3·2)	95 (1·8)	<0·02
Episodic hypoxia present	17/20 (85%)	3/14 (21%)	<0·002

Dip frequency was significantly higher in those with frequent extrasystoles (>10/h) compared with those with infrequent extrasystoles (dip frequency 7·1 (6·0) in those with >10 compared with 3·0 (4·0) dips/h in those with ⩽10 extrasystoles, p < 0·02).

EJECTION FRACTION

In most cases, objective assessment showed poor left ventricular systolic function, with 28/34 (82%) having an ejection fraction of <45% and 16/34 (47%) with an ejection fraction of <30%. The mean (SD) ejection fraction was 26 (13)% (median 25%, range 10%–56%). In three cases, ejection fraction was >50%, although all had been admitted to hospital with dyspnoea requiring diuretic treatment, had an increased cardiothoracic ratio on a chest radiograph, and had evidence of abnormalities of left ventricular wall motion. None of these three patients had hypoxic episodes. There was no difference between the mean ejection fraction in those with grade >III arrhythmias compared with those with grade <III arrhythmias (25 (12)% compared with 27 (14)%).

CORRELATION BETWEEN ARRHYTHMIAS AND OXIMETRY RESULTS

The table shows the relation between severity of arrhythmia (Lown grade >III *v* Lown grades I or II) and dip frequency, mean saturation, and ejection fraction. Saturation dips were more frequent in those with the more severe arrhythmias, whereas the ejection fraction was not significantly different between those with severe and those with less severe arrhythmias. Figure 2 illustrates the poor correlation between ejection fraction and dip frequency, showing that saturation dips are not merely a direct indication of severity of left ventricular dysfunction. A dissociation between clinical severity of disease and oximetry profile was also shown by the fact that the mean dip frequency was no different between the clinically most severe cases (those with class IV NYHA dyspnoea) and those with class III dyspnoea.

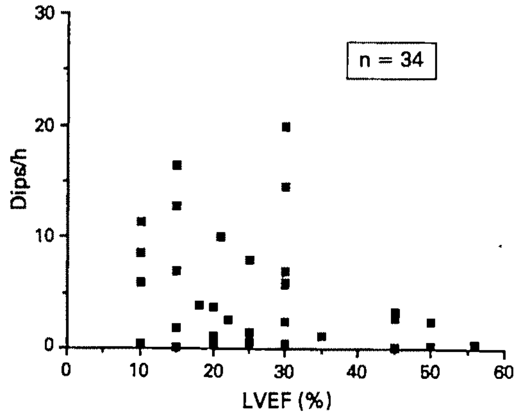


Figure 2 Scatter plot of ejection frequency (LVEF) and dip frequency. There is no correlation between the two variables.

The occurrence of episodic hypoxia was, however, correlated with severity of arrhythmia. The table shows Lown grade >III arrhythmias were only seen in 3/14 (21%) cases where episodic hypoxia was absent but high grade arrhythmias were present in 17/20 (85%) of those with episodic hypoxia.

Figure 3 shows that there was an inconsistent temporal correlation between episodic hypoxia and arrhythmias. In some cases, arrhythmias occurred during or just after hypoxic episodes, whereas in others, considerable episodic hypoxia did not result in arrhythmias. In other cases, arrhythmias occurred without hypoxia.

Discussion

Cardiac arrhythmias have been described during hypoxic episodes in patients with chronic airways obstruction and sleep apnoea,[1 2] but few studies have investigated the relation between nocturnal hypoxia and arrhythmias in those with intrinsic myocardial disease. Otsuka *et al* correlated arrhythmias with oximetry in 81 patients with various cardiac disorders, but patients with left ventricular impairment were not specifically included.[8] Dark *et al* showed an improvement in oxygen saturation after treatment of heart failure in six patients with left ventricular dysfunction, but no analysis of arrhythmia was undertaken.[9] Hanly *et al* carried out oximetry in 10 outpatients with chronic heart failure and showed poor quality of sleep with frequent dips and arousals, but again arrhythmias were not analysed.[10] Takasaki *et al* showed that continuous positive airway pressure treatment improved saturation and left ventricular function in patients with heart failure but again information concerning arrhythmias was not provided.[11] Recently, Davies *et al* published a study of oximetry in 10 patients with heart failure: only one had non-sustained ventricular tachycardia, although this arrhythmia did appear to be temporally associated with a hypoxic episode.[12]

We have carried out arrhythmia and oximetry analysis in 34 patients with impaired left ventricular function. High grade arrhythmias (Lown grade III and above) were common, occurring in 59%. Oximetry showed abnormal patterns in 50% of cases, the mean dip frequency being 4·8 dips/h. A strong correlation was found between the occurrence of high grade arrhythmias and the presence of saturation abnormalities. A total of 17/20 (85%) of those with episodic hypoxia had Lown grade III or higher arrhythmias, whereas only 3/14 (21%) of those without episodic hypoxia had such arrhythmias. Of those 20 patients with Lown grade III or higher arrhythmias, all but three (85%) also had episodic hypoxia. The mean dip frequency was significantly higher in those with high grade arrhythmias than in those without such arrhythmias (6·7 *v* 2·2, p < 0·01).

tion of the diastolic pressure-volume relation, and increases with acute ischaemia. However, the pressure-volume relation itself is influenced by several other factors, such as chamber volume and wall thickness, distensibility, composition and viscosity of the myocardium, pericardial function, atrial contraction, pleural pressure, and coronary vascular volume and pressure.[12]

In this study of segmental ischaemia, changes in left ventricular geometry and filling consistent with increasing chamber stiffness were seen during the first few seconds of ischaemia. The isovolumic relaxation time lengthened and the ascending limb of negative dP/dt became notched at the same time as the onset of asynchrony of anteroseptal left ventricular wall motion. The minimum left ventricular diastolic pressure and the point of inflection of the diastolic pressure curve occurred later in diastole, and rapid early filling was reduced by rigidity and delayed relaxation of the anteroseptal wall. Rapid early filling was further impeded by delayed systolic contraction of the anterior left ventricular wall, which was still moving inward when the mitral valve opened.

There was a small, but statistically significant, increase of 12% in the isovolumic relaxation time within the first seven seconds of LAD occlusion. Left ventricular dP/dt_{min} also fell during the first seven seconds of ischaemia, by 13%, but there was no significant change in left ventricular end diastolic pressure or left atrial pressure. With longer periods of ischaemia the left atrial pressure increased and left ventricular and aortic systolic pressures decreased, resulting in earlier opening of the mitral valve and a reduction in the isovolumic relaxation time.

The total left ventricular relaxation time also began to lengthen early after LAD occlusion, with movement of the nadir of the diastolic pressure wave into later diastole, giving a hammock-like appearance to the diastolic pressure curve. The total relaxation time remained prolonged throughout the ischaemic period, which represents relative failure of ventricular relaxation. The rise in left ventricular filling pressure in association with the hammock-like deformation of the diastolic pressure curve indicates a reduction in diastolic left ventricular compliance. The same phenomenon has been reported during experimental coronary occlusion in dogs.[11]

The effect of reduced diastolic compliance and relative failure of active relaxation of ventricular myocardium is to reduce diastolic filling, particularly the initial phase of rapid early filling. Bonow *et al* showed this phenomenon using radionuclide angiography in patients with coronary artery disease and previous myocardial infarction.[13]

Because the phase of rapid early filling of the left ventricle is impaired during acute ischaemia, the contribution of atrial systole (the terminal phase of left ventricular filling) must become more important. To examine this, Matsuda *et al* studied the left atrial pressure-volume relation in patients with remote myocardial infarction and in controls.[14] They found that the contribution of atrial systole to left ventricular stroke volume was significantly greater in patients with myocardial infarction than in controls. In the present study we also found augmentation of left atrial performance. Left atrial maximum dP/dt increased significantly, implying an increase in the contractility of left atrial myocardium.

This study shows that percutaneous transluminal coronary angioplasty provides a convenient model for the study of myocardial ischaemia in humans. During regional left ventricular ischaemia left ventricular diastolic function, in particular filling, is impaired before any changes in left ventricular ejection occur. The first manifestation of ischaemia of the ventricular myocardium is asynchronous relaxation, which is followed by prolongation of the time taken for global relaxation. The impairment of left ventricular relaxation and filling is offset to some extent by increased atrial contractility and an increase in the atrial contribution to left ventricular stroke volume.

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Nocturnal hypoxia and arrhythmias in patients with impaired left ventricular function

T Cripps, G Rocker, J Stradling

Abstract

***Objectives*—To document the incidence of hypoxic episodes in a series of patients with impaired left ventricular function, and to correlate the occurrence of hypoxia with severity of arrhythmia.**

***Patients*—34 patients with breathlessness and clinical evidence of left ventricular dysfunction.**

***Main outcome measures*—Simultaneous overnight finger oximetry and electrocardiographic monitoring.**

***Results*—High grade arrhythmias (Lown grade >III) occurred in 20/34 (59%) of patients, and frequent dips in oxygen saturation were noticed (mean dip frequency 4·8/h, range 0·1–20·0). 20/34 (59%) of patients had episodic hypoxaemia, including 13/34 (38%) with a classical Cheyne Stokes pattern. There was a correlation between dip frequency and the presence of high grade arrhythmias (those with high grade arrhythmia had mean (SD) 6·7 (5·5) dips/h *v* 2·2 (3·4) in those without, $p < 0.01$); there was also a correlation between the presence of arrhythmias and episodic hypoxaemia (episodic hypoxaemia in those with high grade arrhythmias occurred in 17/20 (85%) *v* 3/14 (21%) of those without arrhythmias, $p < 0.002$). There was no correlation between the presence of high grade arrhythmias or dip frequency and the extent of left ventricular impairment, which was present in all patients (mean (SD) ejection fraction 26% (13%)).**

***Conclusion*—Noticeable abnormalities of nocturnal oxygen saturation occur in patients with impaired left ventricular function, and these are associated with high grade arrhythmias. Interventions that limit desaturation may have valuable anti-arrhythmic effects.**

(*Br Heart J* 1992;68:382–6)

Nocturnal hypoxia due to disordered breathing is described in patients with chronic obstructive pulmonary disease[1,2] and may be associated with cardiac arrhythmias.[3,4] The greatest expression of the arrhythmogenic effect of hypoxia might, however, be expected in those with intrinsic myocardial disease, particularly in patients with impaired left ventricular function, in whom ventricular arrhythmias are frequent and easily precipitated.[5,6] The purpose of this study was to examine fluctuations in nocturnal oxygen saturation in a group of patients with impaired left ventricular function, and to correlate these fluctuations with the occurrence of ventricular arrhythmias and the severity of left ventricular impairment.

Patients and methods

PATIENTS

Patients were selected from those admitted to hospital for elective cardiac catheterisation, or for treatment of refractory chronic heart failure. Those considered to have impaired left ventricular function were identified clinically on the basis of a history of dyspnoea, a cardiothoracic ratio >50% on a chest radiograph, and clinical signs suggestive of left ventricular impairment. All had New York Heart Association (NYHA) grade II-IV dyspnoea. Patients were excluded if they gave a history suggestive of chronic bronchitis, asthma, chronic airways obstruction, or other intrinsic pulmonary disease, but formal lung function tests were not performed. None of the patients had symptoms suggestive of obstructive sleep apnoea, and none were grossly obese (>115% of ideal body weight). Each patient gave informed consent; the study was approved by the hospital ethics committee.

OXIMETRY

Overnight oximetry was performed at the bedside with an Ohmeda Biox 3700 pulse oximeter (version J) and a flexible finger probe.[7] The device's internal memory stores a two digit value at the end of each 12 seconds, which represents the lowest oxygen saturation during those 12 seconds. Thus dips in saturation are not missed but recovery between dips may be underestimated. The 2400 values for oxygen saturation generated over an eight hour period were subsequently downloaded to an IBM compatible personal computer and analysed for mean saturation and dips in excess of 4%. Dips were counted when the saturation fell more than 4% below the previous updated high. No further dip was recorded unless the saturation rose by more than 3%. The probe was applied to the forefinger of either hand late in the evening as the patient was preparing to retire and was removed the next morning. We performed the study on the second or later night in hospital, so that the patient was accustomed to his surroundings, but formal

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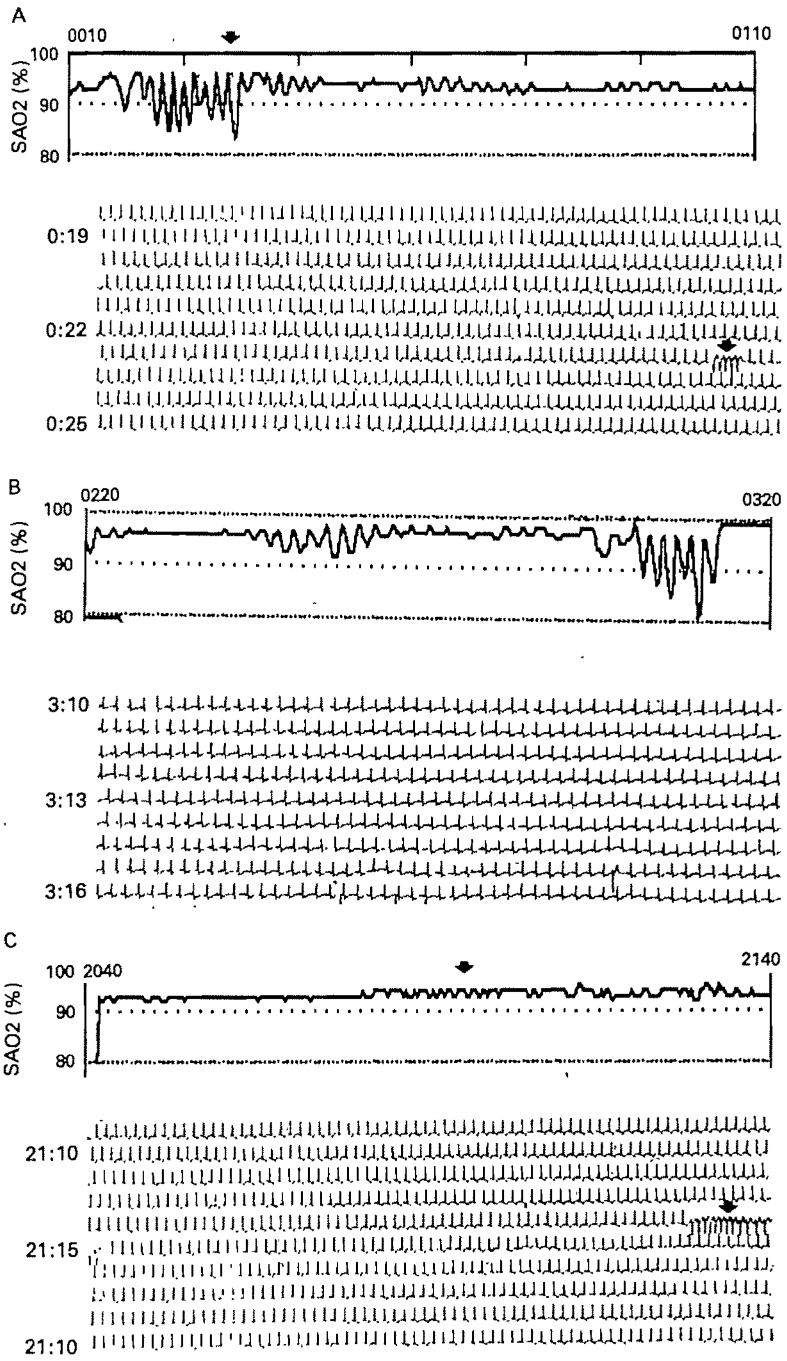

Figure 3 Inconstant temporal correlation between episodic desaturation and arrhythmias. (A) Non-sustained ventricular tachycardia (arrow) occurs between 0023 and 0024 towards the end of an 11 minute period of episodic hypoxia, (B) in a different patient, there is no arrhythmia despite considerable episodic hypoxia between 0310 and 0316; (C) there is non-sustained ventricular tachycardia just before 2113 (arrow) without corresponding hypoxia. Upper trace, oxygen saturation (SAO2); lower trace, pulse rate.

This correlation was, however, not merely a reflection of left ventricular function. The mean ejection fraction was no different between those with and without high grade arrhythmias, and there was also no significant difference between the mean dip frequency in those with grade IV NYHA dyspnoea and those with grade III dyspnoea, confirming the clinical finding that the severest cases were not exclusively associated with episodic hypoxia. It was surprising that three patients were found to have ejection fractions >50% despite a clinical record suggestive of poor left ventricular function. Reversible ischaemia or diastolic dysfunction may have been predominant mechanisms in these cases. These three cases were included in the analysis despite the evidence of good systolic function although none had hypoxic episodes and their inclusion does not materially affect the results.

We have not found a causal relation between nocturnal desaturation and cardiac arrhythmias. High grade arrhythmic activity may occur during or just after a period of episodic hypoxia, but arrhythmias and desaturation episodes may be independent (fig 3). More detailed polysomnographic studies are indicated to elucidate the temporal relations between arrhythmias and episodic hypoxaemia, which probably includes an interaction with other variables, such as the prevailing sympathovagal balance, myocardial ischaemia, and other factors. Nor have we tested the effect of interventions (for example, oxygen treatment) designed to reduce hypoxia on the relations between arrhythmias and oximetric abnormalities. It has been shown that medical treatment of heart failure,[9] administration of oxygen,[10] and nasal continuous positive airway pressure[11] reduce nocturnal desaturation in patients with heart failure, and it might be expected that frequency of arrhythmia would be reduced in patients susceptible to arrhythmias by such measures.

None of the patients we studied had sustained, life threatening arrhythmias during the monitoring period and it is not certain that the non-sustained arrhythmias we found were of prognostic significance. Several studies suggest, however, that such arrhythmias are associated with an adverse prognosis in patients with impaired left ventricular function[13-15] and it might be that correction of nocturnal desaturation would be a more effective way of preventing the development of life threatening arrhythmias than the use of potentially harmful antiarrhythmic agents. Sleep apnoea has been associated with increased mortality in unselected patients after myocardial infarction.[16]

In conclusion, it appears that nocturnal oxygen desaturation is common in patients with severely impaired left ventricular function and that such desaturation is associated with high grade non-sustained ventricular arrhythmias. This association does not, however, seem to be a reflection solely of severity of disease, reflected by left ventricular ejection fraction or NYHA class. Further study is required to find the mechanism of this effect and the result of interventions that limit desaturation upon arrhythmias and prognosis.

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Increased circulating atrial natriuretic factor concentrations in patients with chronic heart failure after inhibition of neutral endopeptidase: effects on diastolic function

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Abstract

Objective—**±Candoxatrilat was used to raise atrial natriuretic factor (ANF) concentrations in patients with heart failure, and the effects on left ventricular systolic and diastolic function were studied to determine the contribution of peripheral and central mechanisms to the haemodynamic effects.**

Design—**This was a single blind, randomised comparison of ±candoxatrilat and placebo in patients with mild heart failure. All patients received two intravenous doses of ±candoxatrilat and two placebo doses on four consecutive days.**

Setting—**A teaching hospital department of cardiology.**

Patients—**Six men (mean age 52 years) with mild heart failure (New York Heart Association class II) due to ischaemic heart disease (four patients) or dilated cardiomyopathy (two patients) were included. Mean ejection fraction was 37·5% and mean peak oxygen consumption was 20·4 ml/min/kg.**

Main outcome measures—**Plasma ANF concentrations, haemodynamic indices and left ventricular diastolic function measured by early to atrial filling rate (E:A ratio) with Doppler echocardiography were determined before and after ±candoxatrilat and placebo.**

Results—**±Candoxatrilat caused a threefold rise of plasma ANF compared with placebo ($p < 0{\cdot}005$), but there was no significant change in heart rate, blood pressure, or cardiac output. Mean right atrial pressure fell from 6·7 to 4·7 mm Hg (NS) and pulmonary artery wedge pressure fell from 9·2 to 6·7 mm Hg ($p < 0{\cdot}05$). Doppler echocardiographic measurements of transmitral blood flow showed a significant fall in peak early left ventricular filling velocity from 39·5 to 34·2 cm/s ($p < 0{\cdot}05$), along with a non-significant rise in peak atrial filling velocity from 39·7–41·6 cm/s after ±candoxatrilat. The E:A ratio, a Doppler index of left ventricular diastolic function, fell from a mean of 1·04 to 0·87 ($p < 0{\cdot}05$).**

Conclusions—**±Candoxatrilat increased plasma ANF concentrations and reduced right atrial and pulmonary artery wedge pressures. No evidence of an improvement in left ventricular systolic or diastolic function was found, so the fall in preload was due to peripheral effects, either an increase in venous capacitance or a fall in circulating blood volume.**

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Atrial natriuretic factor (ANF) is a natriuretic and vasorelaxant peptide hormone secreted from the cardiac atria.[1] Intravenous administration of ANF to patients with chronic heart failure produces a fall in right and left atrial pressure along with a diuresis and natriuresis.[2-5] The cause of the fall in ventricular filling pressures is uncertain, but possibilities include an improvement in left ventricular systolic or diastolic function. Peripheral mechanisms may also be implicated, such as a reduction in plasma volume or an increase in venous capacitance.

A ubiquitous enzyme neutral endopeptidase (endopeptidase 24.11, EC 3.4.24.11, enkephalinase) degrades ANF in vivo. This enzyme is present in high concentration in the lungs and kidneys.[6,7] ±Candoxatrilat (UK 69 578, Pfizer Central Research) is a recently discovered specific inhibitor of this enzyme that has been shown to raise plasma ANF concentrations in animals and human volunteers.[8,9] It is a 50:50 racemic mixture of active and inactive isomers that is poorly absorbed from the gut and therefore has to be given intravenously. The active isomer of ±candoxatrilat is now available as a prodrug with significant oral bioavailability—candoxatril.

We have used ±candoxatrilat to raise plasma ANF concentrations in patients with chronic heart failure. The safety profile and renal effects of ±candoxatrilat in these patients are reported separately.[10] In this paper we describe the acute haemodynamic effects of raising plasma ANF concentrations by endopeptidase inhibition, in particular the effects on left ventricular diastolic function.

Patients and methods

PATIENTS

Six non-oedematous men with clinically mild (New York Heart Association (NYHA) class 2) chronic heart failure were included in this study. Their mean age (range) was 52 (44–61) years and the underlying diagnosis (confirmed by cardiac catheterisation), was ischaemic heart disease in four patients and dilated cardiomyopathy in two. All patients had objective evidence of both impaired left ventricular contractility and reduced exercise capacity. The mean left ventricular ejection fraction on first pass radionuclide ventriculography was 37·5% ((range 28%–44%) normal >50%). The mean exercise time (modified Bruce protocol) was 636 (416–888) seconds, with a peak oxygen consumption 20·4 ((16·0–24·9) normal >25) ml/min/kg.

Patients were excluded if they had any of the following: present or previous hypertension (diastolic blood pressure >100 mm Hg); hypotension (systolic blood pressure <110 mm Hg); atrial fibrillation; primary valve disease; renal impairment (serum creatinine concentration >200 mmol/l); hepatic dysfunction (bilirubin concentration >20).

Approval was obtained from the local hospital ethical committee and all patients gave informed consent to the study.

STUDY DESIGN

Diuretic treatment was withdrawn two days before the study and all other medications were withdrawn for at least seven days. Patients were studied on four consecutive days in hospital and a standard diet containing 150 mmol of sodium was maintained throughout. All studies began at 7.00 am with an oral fluid load of 200 ml of iced water, taken after voiding urine. Fluid balance was maintained during the subsequent 10 hours by voiding every hour and replacing urinary losses by drinking water.

±Candoxatrilat was diluted in 20 ml of isotonic saline before intravenous infusion for 20 minutes. The neutral endopeptidase inhibitor or vehicle alone was given after the second hourly urine collection in a single blind fashion. Blood samples were taken at zero, one, two, four, and eight hours after dosing through an indwelling venous cannula and were analysed for packed cell volume, serum urea, and electrolytes. Plasma ANF was measured by radio immunoassay with an antibody raised locally after extraction in Sep-Pak cartridges, the normal range is 10–50 pg/ml.[11]

On the evening of the second study day a balloon tipped catheter (7F Edwards Laboratories) was inserted through an antecubital vein and positioned in the right pulmonary artery under fluoroscopic control. Measurements of right atrial pressure, pulmonary artery pressure, pulmonary artery wedge pressure, and thermodilution cardiac output (mean of three injections of 10 ml iced injectate, Edwards Laboratories cardiac output computer) were made on study days 3 and 4 at zero, one, two, four, and eight hours after dosing.

Echocardiographic studies were performed by a Hewlett Packard 77020A system with a 2·5 MHz phased array transducer incorporating pulsed wave Doppler. The sample volume was placed in the left ventricle near the tips of the mitral valve in the four chamber view and was positioned to obtain the highest diastolic transmitral flow velocities. Doppler spectral profiles were recorded on video tape and analysed by integral software. The peak velocities during early and atrial diastolic filling were each averaged over 10 consecutive cardiac cycles. The E:A ratio, a Doppler index of left ventricular diastolic function,[12 13] was then calculated as peak early filling velocity:peak late filling velocity.

DOSING SCHEDULE

This was the first study of ±candoxatrilat in patients with chronic heart failure and therefore a wide range of doses, all of which had previously been well tolerated in normal human volunteers, was given. Each dose of ±candoxatrilat or placebo was given on a separate day at around 9.00 am. For safety reasons, initial doses were small and larger doses were administered only if these were well tolerated. Patients were randomised in pairs with the first pair receiving active doses of 10 mg then 20 mg alternating with vehicle alone in random order. Similarly, the second pair of patients were given 50 mg then 100 mg, and the final pair received 200 mg and 400 mg. Because invasive haemodynamic measurements were only made on the final two study days, only the results from these days are shown—that is, doses of 20 mg, 100 mg, and 400 mg.

STATISTICAL ANALYSIS

Data are therefore available for six active and six placebo infusions. They are presented as mean (SEM). The differences between active and placebo infusions were tested for statistical significance with repeated measures analysis of variance and, when indicated, Student's *t* test for paired variables. A probability of <0·05 was taken as statistically significant. Baseline plasma ANF concentrations were positively skewed, and so the ANF data were transformed logarithmically before testing for significance.

Results

No drug related adverse effects occurred after ±candoxatrilat. One patient with a primary

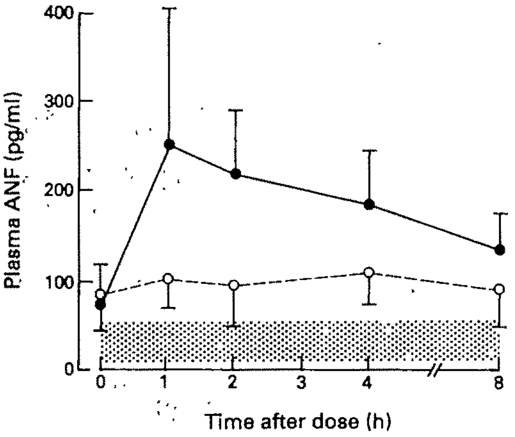

Figure 1 Plasma atrial natriuretic factor concentration (ANF) (mean (SEM)) after ±candoxatrilat (solid lines, n = 6) and vehicle alone (interrupted lines, n = 6). Normal range (10–50 pg/ml) is shown shaded.

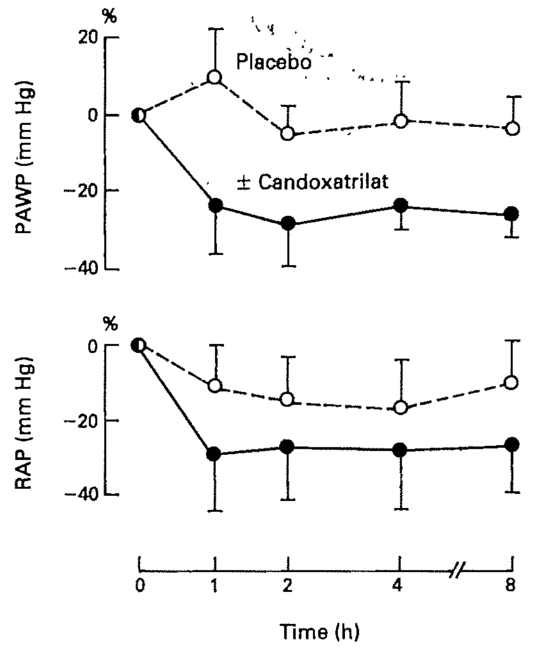

Figure 2 Effects of ±candoxatrilat on pulmonary artery wedge pressure (PAWA) and right atrial pressure (RAP) (mean (SEM)) compared with placebo. Baseline is the mean of two predose measurements 30 minutes apart. Subsequent pressures are expressed as percentage change from baseline.

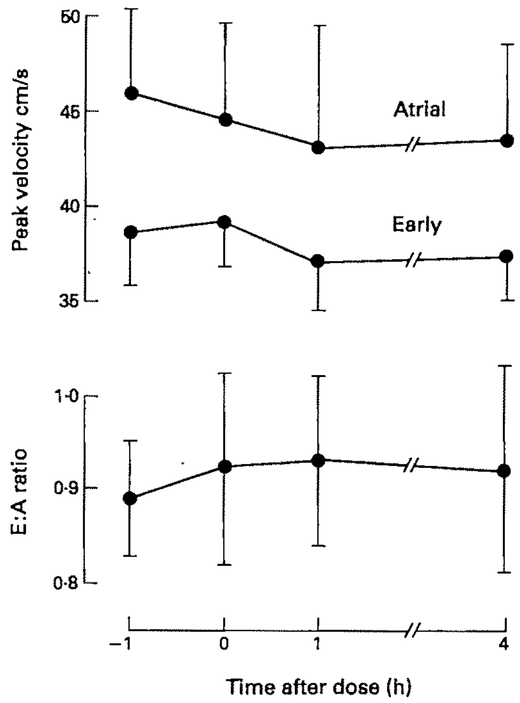

Figure 3 Doppler assessment of left ventricular diastolic function after placebo: mean (SEM) peak early and atrial filling velocities, and E:A ratio.

diagnosis of alcohol related dilated cardiomyopathy and normal coronary arteries developed chest pain two hours after infusion of placebo. This resolved spontaneously. Another patient developed skin inflammation over the course of the Swan-Ganz catheter in the upper arm, necessitating its removal before the final placebo dose. Therefore invasive haemodynamic data are available for five patients after the placebo and all six patients after ±candoxatrilat.

The mean (SEM) plasma ANF concentration was raised at baseline to 80·5 (23) pg/ml (fig 1). After ±candoxatrilat ANF concentrations rose to a peak of 226 (97) pg/ml one hour after the infusion ($p < 0·005$ for difference from placebo). Plasma ANF had returned to baseline by eight hours. The peak ANF concentration did not appear to be dose related over the dose range under study. There was no change after the placebo (fig 1).

HAEMODYNAMIC EFFECTS

The principal acute haemodynamic effect after ±candoxatrilat was a fall in cardiac filling pressures (fig 2). Right atrial pressure fell from 6·7 (2·2) to 4·7 (2·6) mm Hg (NS, $n = 6$) and pulmonary artery wedge pressure fell from 9·2 (1·1) to 6·7 (1·3) mm Hg ($p < 0·05$, $n = 6$). Filling pressures did not change significantly after administration of placebo ($n = 5$).

There were no significant changes in heart rate, systemic arterial blood pressure, cardiac output, or calculated peripheral vascular resistance after ±candoxatrilat or placebo (table). Also, the packed cell volume was not affected by ±candoxatrilat suggesting no change in the plasma volume.

LEFT VENTRICULAR DIASTOLIC FUNCTION

Figures 3 and 4 show the peak velocities of early and atrial transmitral blood flow after placebo and ±candoxatrilat. The peak early and atrial filling velocities did not change significantly from baseline after the placebo, and so there was no change in the E:A ratio. After ±candoxatrilat, however, there was a significant fall in

Effects of ±candoxatrilat on haemodynamics and haematocrit

	Time after dose (h)				
Treatment	*0*	*1*	*2*	*4*	*8*
±Candoxatrilat:					
HR (beats/min)	78 (7)	80 (9)	82 (8)	79 (7)	79 (5)
SBP (mm Hg)	114 (5)	119 (7)	115 (6)	115 (3)	120 (5)
DBP (mm Hg)	76 (4)	78 (3)	79 (3)	78 (3)	79 (4)
CO (l/min)	4·9 (0·4)	5·1 (0·4)	4·6 (0·4)	4·8 (0·4)	4·8 (0·4)
SVR (d/s/cm^{-5})	1328 (92)	1429 (119)	1546 (137)	1446 (98)	1482 (83)
PCV (%)	40·9 (1·8)	42 (2·3)	41·4 (3)	40·9 (1·8)	41·2 (1·7)
Placebo:					
HR (beats/min)	80 (9)	78 (6)	78 (8)	76 (5)	79 (8)
SBP (mm Hg)	116 (8)	115 (7)	114 (6)	116 (7)	117 (8)
DBP (mm Hg)	76 (5)	78 (4)	74 (4)	76 (4)	76 (4)
CO (l/min)	5·1 (0·6)	5 (0·4)	4·9 (0·5)	4·8 (0·5)	5 (0·4)
SVR (d/s/cm^{-5})	1328 (92)	1429 (119)	1546 (137)	1446 (98)	1482 (83)
PCV	40·6 (1·4)	40·4 (1·6)	40 (1·1)	38·1 (1·4)	39·7 (1·4)

Changes in haemodynamics and packed cell volume after ±candoxatrilat and placebo are shown as mean (SEM) for six patients. None of the effects was statistically significant.
HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; SVR, systemic vascular resistance; PCV, packed cell volume.

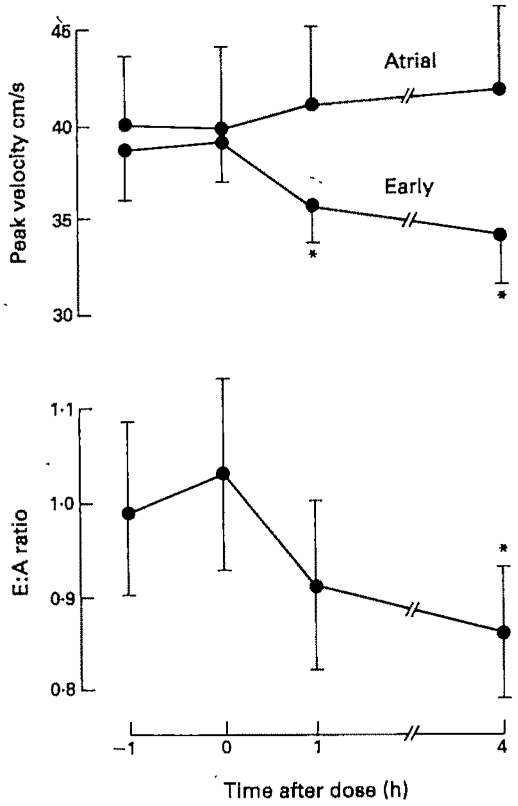

Figure 4 Doppler assessment of left ventricular diastolic function after ±candoxatrilat: mean (SEM) peak early and atrial filling velocities, and E:A ratio.

the mean peak early filling velocity from 39·5 (5·1) to 34·2 (6·1) cm/s ($p < 0·05$), with a rise in peak atrial filling velocity from 39·7 (10·3) to 41·6 (11·2) (NS). The E:A ratio, a Doppler index of left ventricular diastolic function, fell from 1·04 (0·28) to 0·87 (0·22) ($p < 0·05$). This effect is opposite to the predicted response if the falls in filling pressure had been due to improved early left ventricular relaxation. Thus diastolic function did not improve after ±candoxatrilat.

Discussion

The results of this initial, placebo controlled, dose ranging study show that competitive inhibition of neutral endopeptidase by ±candoxatrilat is associated with rises of plasma ANF in patients with mild heart failure. The haemodynamic changes that were found after ±candoxatrilat are very similar to those reported for ANF infusions in patients with chronic heart failure.[2-5] The principal effect was a moderate and prolonged fall in right and left ventricular filling pressures that was still apparent eight hours after dosing, even though the plasma ANF concentration had returned to baseline by this time. A similar prolonged effect has been reported after short-term intravenous infusions of ANF.[2 3] This could be explained by a change in effective blood volume, a sustained interaction between ANF and its receptor, potentiation of other natriuretic peptides (for example BNP), or a second messenger with a more prolonged effect on vascular smooth muscle cells (cyclic guanosine monophosphate).[14]

Possible causes of the fall in filling pressures include an improvement in left ventricular systolic or diastolic performance, a fall in plasma volume, an increase in resistance to venous filling, or a rise in venous capacitance. We did not find any evidence of a positive inotropic effect as there was no rise in stroke volume or cardiac output. A significant fall in plasma volume is unlikely since there was no rise in packed cell volume after ±candoxatrilat. This is, however, a crude method for measuring changes in plasma volume especially when frequent blood sampling for other assays is performed, and it is possible that a small change could have been missed by this technique. Although a fall in plasma volume has been found during ANF infusions in normal volunteers, this has not been reported in patients with chronic heart failure, which lends support to our findings.[4]

A further possible mechanism of the fall in cardiac filling pressures that has received little attention in the past is improved left ventricular diastolic performance, which we assessed non-invasively with Doppler echocardiography. Various conditions that impair left ventricular relaxation, including hypertrophy, ischaemia, and ageing, also reduce the Doppler index E:A ratio.[12 13] This index of diastolic function can be affected by non-myocardial factors, in particular the ventricular loading conditions, which can make interpretation of the E:A ratio in individual patients difficult. Nevertheless it is a useful means of assessing the response to an intervention as long as baseline measurements are available as a control. If the fall in cardiac filling pressures in this study had been due to improved diastolic function, an increase in the E:A ratio would have been expected. In fact the opposite effect was seen. This does not necessarily imply any detrimental effect on diastolic function because the results can be explained by the change in ventricular loading conditions, which would reduce the rate of early diastolic filling. Thus our results do not support a role for an improvement in myocardial systolic or diastolic performance, or a reduction in plasma volume as the cause of the fall in filling pressures produced by ±candoxatrilat. These findings are in keeping with previous experimental experience of ANF infusions.[3-5]

It therefore seems likely that the rise in ANF after ±candoxatrilat had an effect on the peripheral vasculature. In one study of rats it was suggested that an increased resistance to venous filling due to venoconstriction was the cause of the fall in right atrial pressure that occurred during ANF infusion.[15] Studies in man, however, do not support this hypothesis. In vitro experiments on excised large veins in water baths have not shown ANF to have any effect, even in very large doses.[16] Furthermore an in vivo study found that direct infusion of ANF into a dorsal hand vein had no noticeable effect on venous tone.[17] The large veins studied in both of these experiments are not the principal determinants of venous capacitance. This is dependent on the tone of small venules present in the peripheral muscles, and so is harder to determine directly. One study of such capacitance venules in rat cremaster muscle, which had been preconstricted with noradrenaline, showed significant (70%) dilatation with a low concentration of ANF.[18] Therefore we think that the fall in right and left ventricular filling pressures that we have found after ±candoxatrilat, and others have seen during infusion of ANF, is due to dilatation of venous capacitance vessels, although we cannot exclude the possibility of a small fall in effective blood volume.

This study has some limitations. The small number of patients studied leads to a risk of type II error, although the cross over design compensates to some extent. The patients received increasing doses of ±candoxatrilat because we wished to establish the safety of each dose before progressing to a higher dose. This was unavoidable as it was the first study of an endopeptidase inhibitor in patients with heart failure. Consequently only two patients received each dose, so it was necessary to pool the data from different doses to make statistical comparisons possible. We have already discussed the limitations of the Doppler measurement of diastolic function used in this study.

In conclusion, we have shown that inhibition of neutral endopeptidase by ±candoxatrilat leads to a threefold rise in concentration of plasma ANF in mild heart failure. The principal acute haemodynamic effect is a fall in cardiac filling pressures. This was not due to an improvement in left ventricular systolic or diastolic performance, but suggests a peripheral vascular effect.

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Efficacy of flecainide, sotalol, and verapamil in the treatment of right ventricular tachycardia in patients without overt cardiac abnormality

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Abstract

Objective—A comparison of the efficacy of verapamil, sotalol, and flecainide to suppress right ventricular tachycardia (VT) in patients with a clinically normal heart.

Design—Patients underwent treatment serially with verapamil (360 mg daily), sotalol (240 or 320 mg daily), and flecainide (200 or 300 mg daily), (the larger dose was for patients heavier than 80 kg) to suppress tachycardia. Each drug was given orally for five half lives before testing.

Patients—23 patients with right VT associated with a clinically normal heart were studied.

Outcome measures—The effects of drug treatment were examined by the number of ventricular events on 24 hour Holter monitoring, and the ability of tachycardia to be induced by treadmill exercise testing (Bruce protocol) and programmed ventricular stimulation (Wellens protocol), compared with drug free baseline tests.

Setting—Patients were studied in a tertiary referral centre.

Results—All three drugs suppressed ventricular salvos (>3, <5 consecutive ventricular premature contractions) ($p < 0.01$) and VT ($p < 0.05$) on Holter monitoring and did not differ statistically in effect. Exercise induced VT was also suppressed by all three drugs ($p < 0.01$), and of these sotalol was the most effective although this was not statistically significant (14/23 inducible when drug free, 4/23 on flecainide, 2/23 on sotalol, 5/23 on verapamil). Sustained and non-sustained VT induced by programmed stimulation was also suppressed by the three drugs ($p < 0.01$) and again sotalol was the best of these though the differences did not achieve statistical significance (17/23 inducible when drug free, 4/17 on flecainide, 2/17 on sotalol, and 6/17 on verapamil). Proarrhythmic effects of drugs were found in a few patients. There was no difference in the efficacy of the drugs in patients with histological abnormalities of the myocardium when compared with those of normal histology.

Conclusions—Ventricular tachycardia associated with a clinically normal heart can be suppressed by flecainide, sotalol, or verapamil. In individual patients sotalol was the most frequently effective drug (effective in >89% of patients) and is a suitable choice for first line treatment.

(*Br Heart J* 1992;68:392–7)

Most patients presenting with ventricular tachycardia (VT) have easily detectable underlying cardiac disease, such as coronary artery disease, cardiomyopathy, and valvar or congenital heart disease. Five to 10 percent of patients, however, are reported to have no underlying heart disease as suggested by non-invasive and invasive assessment of left ventricular function and coronary anatomy.[1–3] These patients do, however, exhibit variable degrees of histological abnormality on cardiac biopsy (60–90%), including interstitial and perivascular fibrosis and vascular sclerosis, acute or subacute myocarditis, and an increase in interstitial adipose tissue.[4–6] The reports on the prognosis of such patients are contradictory.[7–9] Although most authors suggest that prognosis is good, there are several who indicate that this may be a more common cause of sudden death in young patients than previously proposed.[10–12] Even though treatment may not be indicated on prognostic grounds, many of these patients are severely symptomatic and require treatment to control the tachycardia. Most of the treatment data on these patients consist of short case series and anecdotal reports,[13–15] and there has been no adequate study of the efficacy of anti-arrhythmic drugs in controlling this form of VT. Our study examines and compares the efficacy of flecainide, sotalol, and verapamil in the treatment of VT in patients with apparently normal hearts.

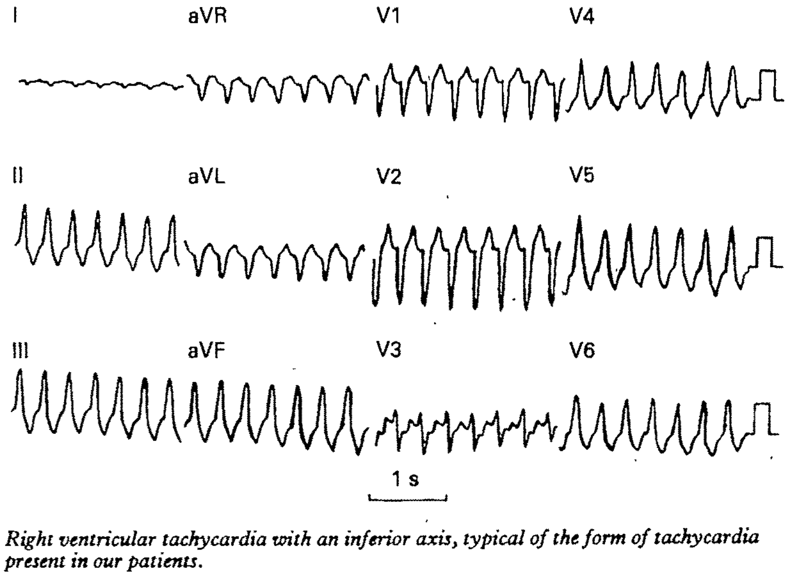
Patients and methods

PATIENTS

Twenty three patients with a clinical history of sustained VT (>30 s) and a clinically normal heart were studied. These patients came from a group of 26 consecutive patients with right ventricular tachycardia seen at our institution over two years. Two patients had had at least two of the drugs used in this study on a previous occasion and these were clinically ineffective. One patient was on amiodarone.

These patients were excluded from our study. Patients gave informed consent to the protocol for drug testing and were enrolled in the study on the basis of the following criteria: (*a*) patients had no history of ischaemic heart disease or congenital cardiac abnormality. (*b*) All had chronic ventricular arrhythmia documented on multiple electrocardiographic leads either during a spontaneous episode or during an exercise test. Arrhythmia was defined as chronic when there was a minimum of two documented episodes at least one month apart. (*c*) Patients had a normal clinical examination, normal chest radiograph (cardiothoracic ratio $<50\%$), and normal resting electrocardiogram (apart from T wave abnormalities). Patients with intraventricular conduction abnormalities, left or right ventricular hypertrophy, and prolongation of the QT interval were excluded. (*d*) No patient had angiographic evidence of coronary artery disease, reduced ejection fraction of the left ventricle, or abnormality of regional wall motion during left ventricular cineangiography as assessed by two independent observers.

All patients had episodes of palpitation, eight had experienced syncope and an additional 11 had had presyncope. The duration of symptoms ranged from two weeks to 20 years. The documented spontaneous arrhythmia was of right ventricular tachycardia (left bundle branch block-like morphology) in all 23 patients (QRS complex >120 ms and predominently negative in lead V1, fig). The frontal plane axis of the clinical tachycardia was defined from the limb leads as leftward ($<-30°$), rightward ($>+90°$), or normal ($-30°$ to $+90°$) from the vector perpendicular to the lead with the most isoelectric QRS complexes. The history of palpitations was suggestive of sustained episodes of VT in all patients with either documented arrhythmia, syncope, or presyncope. The episodes of clinical tachycardia were documented as sustained in 10 patients (spontaneous arrhythmia of uniform QRS morphology lasting >30 s or requiring termination because of haemodynamic compromise) and non-sustained in the rest (uniform broad QRS complexes lasting >3 beats to <30 s and terminating spontaneously without haemodynamic compromise). Despite the non-sustained nature of the arrhythmia in many patients, all patients were severely symptomatic and merited treatment on this basis. The mean (SD) rate of tachycardia was 212 (37·8) beats/min. Patients underwent echocardiographic examination, and all had normal left ventricular function and dimensions. The findings for the right ventricular examination have been published already in a larger group of such patients.[16] Signal averaged electrocardiography was performed on admission and patients also underwent full electrophysiological evaluation before entry in the study. Ventricular endomyocardial biopsies were taken and subjected to routine histopathological studies.



Right ventricular tachycardia with an inferior axis, typical of the form of tachycardia present in our patients.

DRUG TREATMENT

Many of the patients had already received treatment for their tachycardia, but in all, treatment was stopped at least 72 hours before admission and evaluation of the patient in a drug free state. No patient had received amiodarone within three months of assessment. Patients received verapamil (360 mg daily in three divided doses), sotalol (240 mg or 320 mg), and flecainide (200 or 300 mg) daily in divided doses. The larger doses were given to patients who weighed more than 80 kg. The drugs were given serially and maintained for a minimum of five half lives to allow stable concentrations to be reached before evaluation of efficacy. At least five half lives were allowed between drugs to wash out the previous drug. This is therefore an open, non-randomised, fixed sequence drug study. This design was accepted because of clinical and administrative limitations. A fully randomised double blind study would have required matching tablets to be given in random order. Five half lives of the drug with the longest half life would have been necessary at each stage to load and wash out the drugs. This would result in a prohibitively long admission for the patient. The use of the drugs with the shorter half lives initially allowed rapid loading and washout of the drug, reducing the time necessary for the study.

EVALUATION OF TREATMENT

Patients were evaluated with Holter monitoring, exercise testing, and programmed ventricular stimulation when drug free and on each of the three drug treatments. For drug free evaluation, the patient had been on no drugs for at least five days. On each drug, the patient was specifically asked for any subjective side effects experienced during that treatment.

Holter monitoring

Holter tapes (Tracker, Reynolds Medical Ltd, Hertford) were applied for 24 hours and analysed on a commercially available system (Pathfinder III, Mk2, Reynolds Medical). The Holter tape analysis defined the number of normal complexes, ventricular extrasystoles, couplets, salvos (>3, <5 consecutive ventricular premature contractions (VPCs)) and episodes of VT (≥ 5 VPCs at >120 beats/min).

These were then standardised to a one hour recording period before statistical analysis by non-parametric methods. The percentage suppression of ventricular extrasystoles on each treatment compared with those when drug free was also calculated. The number of patients in whom >75% and >90% suppression of Holter events was achieved is also given.

Exercise testing

Exercise tests and programmed ventricular stimulation (see next section) were performed two to four hours after the last dose of the drug. Treadmill exercise testing was performed with the Bruce protocol[17] and the electrocardiogram was monitored during the test with apparatus from Marquette Electronics (Milwaukee, USA). Patients exercised until maximal predicted heart rate was achieved, became limited by dyspnoea and fatigue, or had sustained VT. Electrocardiographic recordings (leads II, V2, and V5) were monitored during the test and for a minimum of 10 minutes after exercise or until the cardiac rhythm returned to the pre-test sinus rate. Blood pressure and the 12 lead electrocardiogram were recorded before, and immediately after the exercise and every three min during exercise and recovery. Exercise provoked tachycardia was defined as the presence of five or more consecutive ventricular extrasystolic depolarisations occurring during or after exercise and was considered sustained if it lasted 30 seconds or longer. Changes in ST segment were monitored throughout the test, but no patient had any changes to suggest ischaemia.

Programmed ventricular stimulation

Programmed ventricular stimulation was performed after an overnight fast. After giving 10 ml of 1% lignocaine for local anaesthesia, multipolar electrode catheters were inserted through the subclavian vein into the atrial appendange and right ventricular apex. The intracardiac electrograms and surface electrocardiograms were displayed simultaneously on a multichannel oscilloscope and recorded on a multichannel inkjet recorder (Siemens Mingograph, Solna, Sweden) at a paper speed of 25–100 mm/s. Ventricular stimulation was performed with a Medtronic 5326 programmable stimulator (Medtronic, Minneapolis, USA) with 1·8 ms rectangular pulses at twice diastolic threshold. Programmed ventricular stimulation was performed by the Wellens protocol.[18] Briefly, one premature ventricular stimulus was introduced after every eight paced or conducted ventricular QRS complexes beginning late in diastole and then at progressively closer coupling intervals until ventricular refractoriness was encountered. The extra stimulus coupling interval was then increased by 20 ms, out of ventricular refractoriness and a second extra stimulus was introduced. The process of diminishing coupling intervals was repeated for the second and then the third extra stimulus until a total of three extrastimuli had been introduced. Paced drive cycle lengths of 600, 500, and 400 ms were used. If VT was not induced by the 12 stages of Wellens protocol, isoprenaline was infused at a rate of 1–4 μg/min to increase the sinus rate by at least 30% or to 120 beats/min (whichever was less) and the programmed ventricular stimulation was repeated. The test was considered positive if VT of the same configuration and axis as the clinically documented tachycardia was induced. If other configurations of tachycardia were induced, then the test was considered non-specific and negative. Inducible non-sustained VT was defined as ventricular extrasystoles of uniform QRS configuration, rate >120 beats/min, lasting ⩾5 beats and <30 s, and terminating spontaneously without haemodynamic compromise. The tachycardia was defined as sustained if it lasted >30 s or required termination because of haemodynamic compromise. If the study did not induce VT in the drug free state, even after the use of isoprenaline, a further study was performed the next day. If in this study, VT could not be induced after giving isoprenaline and 120 μg atropine, further programmed stimulation was not performed during the evaluation of the drugs.

Statistical analysis

Statistical analysis was performed with the SPSS package (SPSS Inc, Chicago, USA). Inducibility of the tachycardia was assessed when drug free and on each of the drug treatments for each patient. Differences between the results when drug free and during treatment with the three drugs were compared by analyses of variance, contingency tables, and non-parametric analyses as appropriate.

Results

Twenty three patients (12 men) mean age 42·6 (SD 11·8; range 21-69) years were studied. All patients had right VT of which 11 had a rightward axis, four had a leftward axis, and eight had a normal axis. The mean (SD) doses of the drugs given were 233 (64·3) mg flecainide, 270 (48·2) mg sotalol, and 360 (0·0) mg verapamil. Table 1 shows the results of the Holter monitoring. There was a large individual variability in the number of ventricular extrasystoles in the 24 hours, but the effects of the different drug treatments were fairly consistent. All three drugs resulted in partial suppression of ventricular extrasystoles, couplets, salvos, and episodes of VT on Holter monitoring. The numbers of patients with 90% and 100% suppression of VT on Holter monitoring were similar on the three drugs (table 1). The drugs did not differ statistically in efficacy. The comparative ineffectiveness of flecainide in reducing Holter monitored events contrasts with previous reports of its efficacy in other types of VT. An increase in the hourly episodes of VT >150% over drug free values was seen in one patient on flecainide, one patient on sotalol, and two patients on verapamil.

Table 2 gives the results of exercise testing The time to the end of the test, whether this was by exhaustion, achievement of the maximum heart rate, or start of tachycardia, was not affected by any of the treatments. The time to

Table 1 *Results of Holter monitoring and the number of patients with suppression of Holter monitored events when drug free and on three treatments*

	Drug free (n = 21)	*Flecainide (n = 21)*	*Sotalol (n = 21)*	*Verapamil (n = 21)*	*p Value*
VES/h	741·7	269·3	446·4	487·7	0·07
Couplets/h	28·8	19·9	8·3	7·5	0·06
Salvos/h	4·9	0·4	9·3	4·8	0·007
VT/h	12·8	0·1	2 8	3·3	0·04
No of patients with >75% suppression of:					
VES/h		7	5	6	
Couplets/h		10	9	8	
Salvos/h		9	9	7	
VT/h		10	10	9	
No of patients with >90% suppression of:					
VES/h		3	4	5	
Couplets/h		9	7	6	
Salvos/h		9	9	6	
VT/h		10	10	9	
No of patients with 100% suppression of:					
VT/h (total n = 13		9	9	8	

Data are on 21 patients because of tape failures on two. VES, ventricular extrasystoles.

the end of the test on sotalol did not differ significantly from the other treatments although it was a little lower. Fourteen patients developed exercise induced VT when drug free and in four the arrhythmia was sustained. All three drugs resulted in some suppression of exercise induced VT and there were only two episodes of sustained tachycardia, one on sotalol and one on verapamil. Two patients on flecainide, one patient on sotalol, and three patients on verapamil had VT at exercise on the drug when there had been no arrhythmia when drug free (table 3). This may be due to the inherent variability of induction of arrhythmia with exercise or a genuine proarrhythmic effect. Sotalol was the best of the three drugs but this difference was not significant (p = 0·4). The stage at which tachycardia was induced was not significantly influenced by the treatments (p = 0·4 for all treatments), though more patients had tachycardia during the test rather than in recovery on flecainide and verapamil when compared with sotalol.

Tachycardia was induced by programmed ventricular stimulation in 17 patients when drug free, in all cases only tachycardia that was of similar configuration and axis to the clinical tachycardia was considered relevant. In one patient the clinical tachycardia was only stimulated after isoprenaline infusion (2 μg/min) when drug free and the same dose of isoprenaline was used on all the subsequent trials with antiarrhythmic treatment. In seven patients, the induced tachycardia was sustained. Inducible tachycardia was rendered non-inducible by all three drug treatments in over 50% of the patients (table 4). Although flecainide when compared with sotalol made fewer patients non-inducible (13/17 *v* 15/17) and non-sustained (2/7 *v* 6/7) these differences were not significant (p = 0·4 and p = 0·9). More patients were inducible (6/17) and sustained (4/7) on verapamil when compared with sotalol (p = 0·07 and p = 0·8 respectively). If the induction and suppression of only sustained VT was considered, the results were similar and all three drugs suppressed inducible VT, but did not achieve statistical significance because of the small numbers. The stage of the Wellens protocol at which tachycardia was induced was also increased by all three treatments (p < 0·01) but no difference could be shown between the treatments (p = 0·4; data not presented). Two patients on flecainide, one patient on sotalol, and three patients on verapamil developed sustained VT on the drug, whereas VT in these patients had been non-sustained when drug free. In one patient the induced tachycardia was faster on sotalol than the drug free arrhythmia and required cardioversion, whereas two of the tachycardias induced on verapamil were haemodynamically unstable, requiring cardioversion. Side effects from the drugs included five patients who experienced dizziness on flecainide and six said they were tired on sotalol. Two patients had some tiredness on verapamil. Individual patients responding to one drug, in general responded to the other drugs and there was no difference in the efficacy of the drugs in patients with abnormal histology compared with those with normal histology in any of the three tests.

Discussion

The results suggest that right VT associated with a normal heart responds well to the drugs

Table 2 *Results of exercise testing when drug free and with three drug treatments*

	Drug free (n = 23)	*Flecainide (n = 23)*	*Sotalol (n = 23)*	*Verapamil (n = 23)*
Exercise tolerance	599	627	617	643
(SD)	(199)	(169)	(201)	(153)
Non-inducible*	10	20	22	19
Inducible*	14	4	2	5
Sustained tachycardia*	4	0	1	1
p Value†		0·007	<0·001	0·02

*Number of patients.

†For differences between the drug treatments and drug free for induction of ventricular tachycardia (VT).

Table 3 *Number of patients with or without ventricular tachycardia (VT) during exercise when drug free and in three treatment groups*

	Flecainide	*Sotalol*	*Verapamil*
No VT baseline No VT drug	7	8	6
VT baseline No VT drug	12	13	12
VT baseline VT drug	2	1	2
No VT baseline VT drug	2	1	3

Table 4 Results of programmed stimulation when patients were drug free and in each of three treatments groups

	Drug free (n = 23)	*Flecainide (n = 17)*	*Sotalol (n = 17)*	*Verapamil (n = 17)*
Non-inducible*	6	13	15	11
Inducible*	17	4	2	6
Sustained tachycardia*	7	2	1	4
Mean rate of tachycardia† (beats/min)	241·0	213·3	230·0	220·0
p Value‡		0·004	<0·001	0·03

*Number of patients; †rate during induced sustained VT; ‡p value for differences between drug treatment and drug free for induction of tachycardia.

tested in this study. Although differences between the drugs did not achieve significance, sotalol was generally the most effective.

Earlier studies of the treatment effects of drugs in VT associated with a normal heart are few. Buxton *et al* examined the effect of antiarrhythmic drugs upon spontaneous arrhythmia in right ventricular tachycardia and reported that class 1 antiarrhythmic agents (procainamide, quinidine) suppressed all VT in 9/16 patients and were ineffective in seven.[3] Propranolol suppressed spontaneous VT in 8/16 patients whereas verapamil was effective in 1/4. Amiodarone was used in 2/4 patients and two were not suppressed by any form of drug treatment. Ventricular tachycardia inducible by programmed stimulation was rendered non-inducible in 8/9 patients by class 1 agents, in 3/6 patients by propranolol, and in 0/4 patients by verapamil. Rahilly *et al* reported a series of patients with repetitive monomorphic VT associated with a normal heart, which included patients with VT of right and left ventricular origin in whom 7/7 patients responded to enacainide.[19] Five other patients received either quinidine or propranolol singly, combined, or aprinidine. Six patients with right ventricular outflow tachycardia reported by Pietras *et al* were evaluated by serial treadmill testing.[13] In these procainimide, quinidine, and disopyramide were relatively ineffective whereas propranolol prevented treadmill provocation of VT in all patients. Similar results were obtained by Brodsky *et al* where in six patients, treatment with β blocker prevented induction of VT by exercise and programmed stimulation and reduced ventricular extrasystoles and VT on Holter monitoring.[14] Lemery *et al* in their series of VT of right and left ventricular origin reported that most patients (48%) were treated with either sotalol or a class IC agent, whereas amiodarone was used in 19%, and a calcium channel blocker was used in two patients.[9] In a specific study of right ventricular tachycardia, sotalol was reported as effective as were class IC agents, whereas verapamil was effective in only one patient.[15] These studies contrast with the present report where a single configuration of VT has been studied and preselected drugs used at fixed doses.

Our study is not a randomised controlled trial, and therefore, it is difficult to ascertain placebo effects, elements of bias, and carry over effects. Although it is straightforward to organise and conduct a study of two drugs in a double blind placebo controlled manner, a trial involving three drugs and a placebo presents considerable logistic difficulties. The study does not include drug concentrations and although sotalol and flecainide have somewhat long half lives, that of verapamil is variable. Furthermore, verapamil is subject to substantial first pass metabolism. To minimise variation due to these factors, exercise tests and programmed stimulation were performed two to four hours after the last drug dose. The tests used for evaluation of drug efficacy in this study are not subject to bias, and adequate periods were allowed for the drug concentrations to equilibrate and wash out. This study, despite its deficiencies, is the only systematic study of drug efficacy in the suppression of VT associated with a normal heart. A study of this nature does, therefore, provide valuable information allowing appropriate choice of drug for patients with this form of tachycardia.

All patients had left bundle branch block-like morphology VT, which can usually be mapped to the right ventricle[3] and is often from the region of the outflow tract when associated with a rightward or normal axis. Electrophysiological mapping of the tachycardia of patients in this study was performed in eight cases and this showed the origin of the tachycardia to be in the right ventricle or the septal aspect of the right ventricular outflow tract in seven subjects and in the free wall of the outflow tract in one. Our experience with these forms of tachycardia is similar to that of other groups in that they are often inducible by exercise and less frequently by programmed ventricular stimulation.[7-9]

Whether this form of tachycardia requires treatment, and the prognosis of VT associated with a normal heart remain controversial issues. Many studies suggest that when VT occurs in association with a normal heart prognosis is good and the patients do not suffer sudden death.[2 7 8] This contrasts with VT associated with ischaemic heart disease and cardiomyopathy where there is a high mortality associated with symptomatic VT. There are, however, several studies reporting that prognosis of VT in young patients with "normal" hearts may be worse than previously proposed.[10-12] Many of the patients in these groups had frank arrhythmogenic right ventricular dysplasia, and most had right VT. Though none of our patients had obvious evidence of arrhythmogenic right ventricular dysplasia, many patients showed evidence of endocardial and interstitial fibrosis, and some had fatty infiltration of the myocardium, which may represent variant forms of this condition. Future studies need to concentrate on the classification of VT associated with a normal heart and the natural history of the tachycardia in these subgroups. In our own series of 40 patients with VT associated with a normal heart followed up for a period of three years, there have been two deaths, one related to surgery for incessant VT, and the other a sudden death, presumably related to arrhythmia. This mortality is higher than that expected in such a young group of subjects suggesting that the condition may not be as benign as reported in previous studies.

Although many patients may be more or less symptom free some have severe symptoms and suffer disabling attacks of palpitation. All the patients in this study had evidence of sustained episodes of VT with symptoms of sustained palpitation, syncope, or presyncope related to arrhythmia. Thus although some patients with only non-sustained episodes of palpitation may not require drug treatment, many will have disabling symptoms necessitating treatment. Our study and the clinical experience of other groups suggest that these tachycardias are suppressed by the β blocking and class III activity of sotalol, the class IC effect of flecainide and the class IV action of verapamil. In this study the effect of a pure β receptor blocking agent was not examined, but there are three previous reports of its efficacy.[13 14 20] Overall, sotalol was the most effective drug in suppression of the tachycardia in these patients, although flecainide was similar. Verapamil was not as effective as the other two agents.

Although there is variability of the response to the test used to assess efficacy of treatment, our study appears to show that proarrhythmic effects may occur in this patient group; some patients developed exercise induced VT whereas these had been free of arrhythmia when drug free; some with non-sustained VT when drug free became sustained and haemodynamically unstable on the drug during programmed ventricular stimulation. Patients will therefore require careful assessment before the introduction of long-term drug treatment. Patients who responded to one drug were, in general, responsive to the other agents used in the study. There were, however, some patients in whom one agent was effective whereas there was no response to the others. Sotalol was well tolerated as treatment in the group as a whole with few side effects. It therefore seems reasonable to treat such patients with sotalol as first line treatment and use other agents only when this fails. The responsiveness of some of the patients in this group to verapamil is interesting as it suggests that some of these tachycardias may be due to triggered activity rather than to a re-entry mechanism.[21] There are no publications concerned with how efficacy of drugs should be assessed in this group. Our data suggest that patients who have therapeutic suppression of exercise induced VT, and VT induced by programmed stimulation, also have good control of Holter monitored events and symptoms, suggesting that all three methods of monitoring efficacy may play a part in the mangement of such patients.

We conclude that VT associated with a normal heart responds well to all three forms of drug treatment used in this study. The most efficacious agent for suppression of exercise induced and VT induced by programmed ventricular stimulation appears to be sotalol. Flecainide and verapamil can be used in cases where sotalol has failed.

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Comparison of unipolar and bipolar ventricular paced evoked responses

M W Baig, J C Cowan, E J Perrins

Abstract

***Objectives*—To study the differences between endocardial bipolar and unipolar ventricular paced evoked responses and surface electrocardiograms.**

***Patients*—10 patients with conduction system disease awaiting insertion of a permanent pacemaker were studied with temporary ventricular pacing from the right ventricular apex.**

***Main outcome measure*—Comparison of the durations of the QRS complexes and QTa and QTe intervals of the endocardial bipolar paced evoked response and the surface electrocardiogram with those of the reference unipolar paced evoked response.**

***Results*—By comparison with the unipolar reference, the mean durations of the QRS complexes of the bipolar signal and the surface electrocardiogram were 41·8% and 132·1% respectively. The mean QTa interval was 85·9% and 112·2% respectively and the mean QTe interval was 86·9% and 109·5% respectively. All these differences were significant. The amplitudes of the unipolar QRS complexes and T waves were significantly larger than those recorded in the bipolar configuration.**

***Conclusions*—Differences between the unipolar and bipolar ventricular paced evoked responses are significant. The time course of the unipolar signal is closer to that of the surface electrocardiogram. This indicates that the unipolar paced evoked response does not reflect local electrophysiological events, as has been suggested previously.**

(*Br Heart J* 1992;68:398–402)

The ventricular paced evoked response was first described in 1981 and has been used to provide the sensor for the QT sensing, rate adaptive pacemaker.[1] The paced evoked response is recorded conventionally as a unipolar signal with the negative pole within the heart and the positive pole, which is usually the case of the pacemaker, at a variable distance on the body's surface. Previous studies have noted that the interval between the pacing stimulus and the apex of the evoked T wave corresponds roughly to the time to 90% repolarisation of a locally recorded monophasic action potential.[2 3]

Consequently, it has been assumed that the paced evoked response reflects the duration of local action potential and that it might provide an easy measurement of local ventricular repolarisation as an alternative to the monophasic action potential. By its nature, however, a unipolar electrogram contains both local and far field components.[4] Previous investigators have cautioned against using unipolar signals to determine local electrophysiological events.[5] By contrast, both poles of a bipolar system are located within the same cardiac chamber, and this type of electrogram is inherently more suited to the assessment of local depolarisation and repolarisation.

The aims of this study were to compare the characteristics of simultaneously recorded bipolar and unipolar paced evoked responses and to assess the relative contributions of local and global myocardial depolarisation and repolarisation to the morphology of the unipolar paced evoked response.

Patients and methods

PATIENT SELECTION

Ten patients (mean age 66·3 years; six men) were studied. Five had complete heart block, and the rest had sick sinus syndrome. In all cases standard (6F USCI) bipolar temporary pacing electrodes had been inserted before permanent pacemakers were implanted, and temporary pacing was performed from the right ventricular apex. None of the patients had a history of myocardial infarction or were taking any drugs likely to affect cardiac electrophysiology. Studies were performed in the postabsorptive state after informed consent had been obtained.

RECORDING OF THE PACED EVOKED RESPONSE

A large adhesive defibrillator pad (surface area 178 cm^2) placed over the right scapula served as the remote, indifferent electrode. Unipolar stimulation was used in all cases. This is the standard method of cardiac stimulation as the wide distance between electrodes reduces residual polarisation potentials and facilitates sensing of the paced evoked response. A dedicated external pulse generator is needed to record the paced evoked response.[6] This delivers a modified pulse waveform that, together with inbuilt circuitry for automatic postpulse compensation, eliminates the polarisation potential that is generated at the interface between the myocardium and the electrode.[7 8] The pulse generator contained two identical sensing amplifiers, which enabled

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simultaneous recording of the unipolar and the bipolar paced evoked responses being recorded between the tip and ring electrodes (separation 10 mm) of the pacing lead. The output of the pulse generator was set to twice the diastolic threshold with a pulse duration of 0·5 ms, and the rate was fixed to ensure continuous capture.

For patients with complete heart block the pacing rate was 70 beats/min. For patients who had sinoatrial disease faster rates were necessary to ensure continuous pacing (80–110 beats/min), although the minimum overdrive pacing rate was used to minimise the potential adverse haemodynamic effects and their associated autonomic reflexes. These may occur with ventricular pacing in this group of patients and could have affected the values studied. Electrograms were recorded on a chart recorder (Gould ES 1000) at a paper speed of 100 mm/s after a minimum of three minutes of pacing to ensure stabilisation of the myocardial repolarisation time.[9 10]

The endocardial electrograms were compared with the complexes of the standard 12 lead surface electrocardiogram recorded in turn together with the simultaneous unipolar and bipolar paced evoked responses. There is no generally accepted method for selecting leads for measuring the QT interval. Therefore, to standardise the measurement technique in our study the criteria for selecting the surface electrocardiogram lead that was to be compared with the paced evoked responses were that it should show a clearly defined T wave and the least difference in total duration when compared with the unipolar paced evoked response. The second criterion used minimised the probability of detecting a significant difference between the QT intervals of the evoked response and the surface electrocardiogram. Consequently, measurements of the surface electrocardiogram were made most frequently from leads V1 and V2. Right ventricular apical pacing produced the expected pattern of left axis deviation and complete left bundle branch block in all cases.[11]

DEFINITIONS AND MEASUREMENTS

Evoked QRS complex

In the paced evoked response the initial deflection after the pacing stimulus is negative (evoked QRS complex) and denotes spread of the depolarisation wavefront away from the stimulating electrode; it is followed by a positive evoked T wave (fig 1). The duration of the evoked QRS is a measure of total ventricular depolarisation time in the area of the heart subtended by a sensing dipole, and it depends on the separation of the dipole.[12] The duration of the evoked QRS, defined as the interval between the pacing stimulus and the end of the S wave—that is, the point when the isoelectric line is crossed[13] was measured for the simultaneous bipolar and unipolar paced evoked responses and from the surface electrocardiogram lead.

Evoked QT intervals

The QT interval is the standard clinical measure of ventricular repolarisation time. It was measured from the pacing artefact to the terminal T wave deflection (QTe) by standard criteria, in which the end of the T wave is defined as the intersection of the tangent drawn through the point of maximum downslope of the T wave with the isoelectric line.[14 15] The QTa was defined as the interval between the pacing stimulus and the apex of the T wave (fig 1).[15]

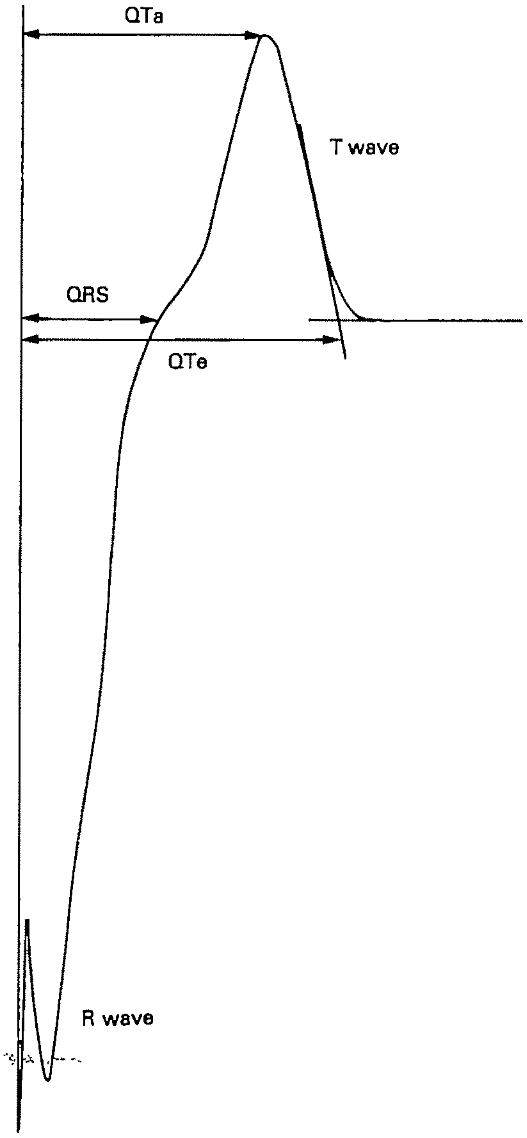

Figure 1 Components of unipolar ventricular paced evoked response, showing definitions of QRS, Q to apex of T (QTa), and Q to end of T (QTe) intervals.

Amplitude of evoked QRS complexes and T waves

The amplitudes of the evoked QRS complexes and T waves were measured from the isoelectric line for the simultaneous unipolar and bipolar signals and the average value calculated by reference to a 5 mV calibration signal.

STATISTICAL ANALYSIS

The simultaneous evoked QRS and QT intervals of the bipolar and unipolar paced evoked responses and the selected lead of the surface electrocardiogram for five consecutive beats were measured and the average interval calculated. The QRS and QT intervals of the

Table 1 Standardised durations of QRS complexes and QT intervals of simultaneously recorded bipolar paced evoked response (PER) and surface electrocardiogram (ECG) with respect to unipolar PER (values are percentages of PER)

	Bipolar			*Surface ECG*	
	Mean	*(SD, range)*	*Unipolar*	*Mean*	*(SD, range)*
QRS	41·8	(16·4, 22–69)	100	132·1	(16·3, 101–158)
QTa	85·9	(1·9, 83–88)	100	112·2	(3·1, 109–115)
QTe	86·9	(3·6, 83–93)	100	109·5	(5·8, 102–118)

Analysis of variance with p < 0·01 for comparison of QRS intervals gave F_{crit} = 5·49 and F_{obs} = 117·6 and for comparison of QT intervals, F_{crit} = 5·49 and for QTa F_{obs} = 161·8 and for QTe F_{obs} = 83·4 (see text for explanation of terms).

Table 2 Comparisons of amplitudes (mV) of QRS complexes and T waves of simultaneously recorded bipolar and unipolar paced evoked response (PERs) by paired t *test*

	Bipolar PER		*Unipolar PER*		
	Mean	*(SD, range)*	*Mean*	*(SD, range)*	*p Value*
QRS complex	9·9	(3·8, 3·7–17·6)	13·5	(3·4, 8·3–19·8)	<0 001
T wave	2·6	(1·4, 1·1– 4·8)	5·7	(1·9. 2·6– 7·1)	<0·002

bipolar paced evoked response and the surface electrocardiogram were standardised as a percentage of the values of the unipolar paced evoked response to take account of differences in the pacing rate between patients. The difference between intervals was assessed by one way analysis of variance. Results were assessed by comparing the p values and the computed value of the test (f_{obs}) with the critical value (F_{crit}). The value of F_{crit} for these data was 5·49; values of F_{obs} greater than this indicate a significant difference. Table 1 summarises the mean (SD) values of the intervals under study.

The mean amplitudes of the evoked QRS complexes and T waves of the bipolar and unipolar evoked responses were calculated with reference to the 5 mV test signal. The results were analysed with Student's paired *t* test and are expressed as means (SD). Significance was inferred if p < 0·01, and the 95% confidence intervals (95% CI) were calculated (table 2).

Results

COMPARISON OF EVOKED QRS DURATIONS

The duration of the measured QRS interval increased progressively from the bipolar to the unipolar paced evoked response and from this to the measurements made from the surface electrocardiogram (table 1 and fig 2). Analysis of variance indicated that the durations of the QRS complexes of the bipolar paced evoked response and the surface electrocardiogram differed highly significantly from that of the unipolar evoked response (F_{obs} = 117·6, p < 0·0001, where F_{crit} = 5·49 at the 5% level). The differences in absolute terms were less between the unipolar paced evoked response and the surface electrocardiogram (32·1%) than those between the two paced evoked responses (58·2%). This suggests that the unipolar paced evoked response more closely resembles the surface electrocardiogram and therefore reflects a depolarisation wavefront recorded over a larger area than the local electrical activity recorded by the bipolar paced evoked response.

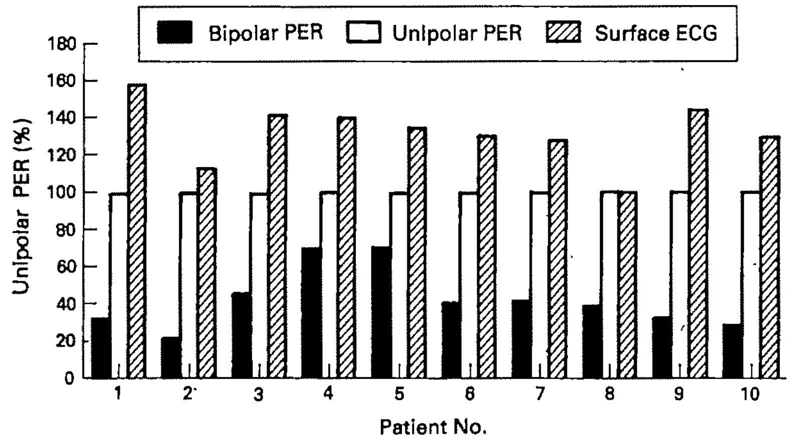

Figure 2 Relative durations of QRS complexes of bipolar and unipolar paced evoked responses (PER) and surface electrocardiogram (ECG). Values have been standardised with reference to unipolar PER.

COMPARISON OF THE EVOKED QT INTERVALS

The changes in the QTa and QTe intervals showed a similar pattern to that for the duration of the QRS interval (table 1, fig 3a and b). The differences in the mean durations of the QTa and QTe intervals of the bipolar evoked response (QTa 14·1%, QTe 13·1%) and the surface electrocardiogram (QTa 12·2%, QTe 9·5%) were similar when compared with the unipolar evoked response. For the QRS component these differences in the QT intervals were highly significantly different (for QTa intervals F_{obs} = 161·8, p < 0·0001; for QTe intervals F_{obs} = 83·4, p < 0·0001, where F_{crit} = 5·49).

AMPLITUDES OF THE EVOKED QRS AND T WAVES

The difference between the mean amplitudes of the bipolar and unipolar paced evoked QRS complexes was −3·49 mV, with a 95% CI of −4·7 to −2·3 mV (p < 0·001). Similar significant differences were found for the mean evoked T wave amplitudes. The difference between the mean amplitudes of the bipolar and unipolar evoked T waves was −3·08 mV, with a 95% CI of −4·4 to −1·7 mV (p < 0·002).

Discussion

The main bioelectrical events of ventricular electrograms are the intracardiac QRS complex, the intracardiac T wave, and any possible superimposed injury current. The first two components have been discussed in detail. Six of the temporary electrodes had been in place for more than 48 hours, and any injury current had probably resolved.[16] Our previous work in which the reproducibility of the relation between the paced QT interval and rate has been examined with an interval of not less than 24 hours has shown no significant difference in the morphology of the paced evoked response. Furthermore, ST segment shift is unlikely to have affected the measurements made in this study.

Electrocardiograms are the net result of the electric currents generated by ion exchange across cardiac cell membranes. The heart gen-

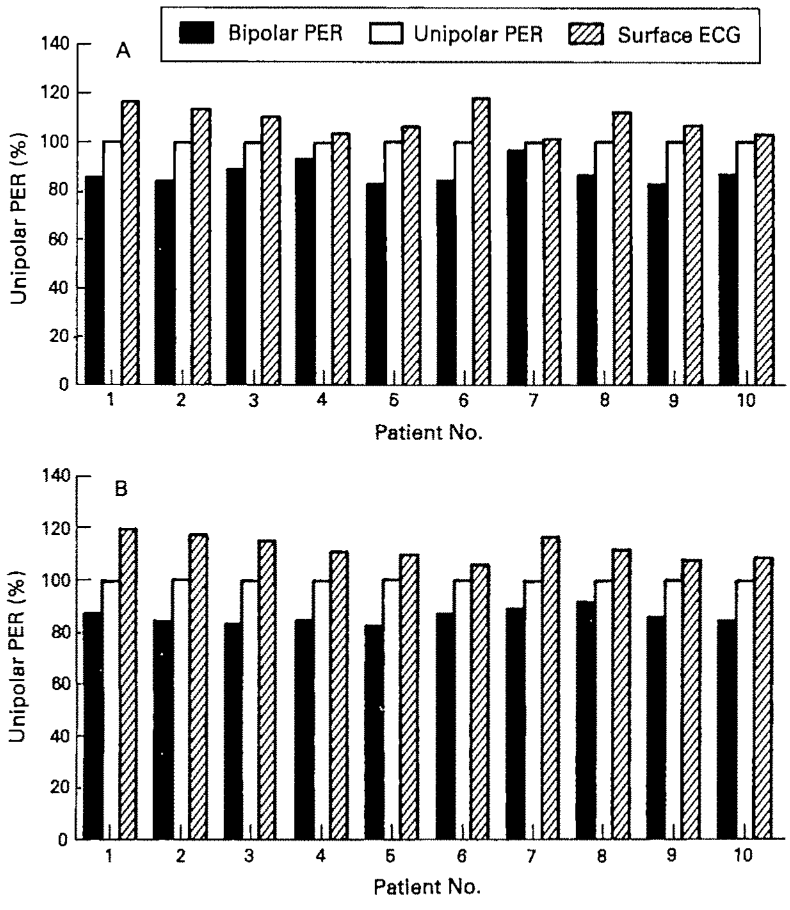

Figure 3 Relative durations of (A) QTa and (B) QTe intervals of bipolar and unipolar paced evoked responses (PERs) and surface electrocardiogram (ECG). Values have been standardised with reference to unipolar PER.

erators complex signals, and the addition of a surface electrode introduces further complexity; the intervening thorax and boundaries (skin-air, and intracavity blood mass within the heart) are non-homogeneous conductors, and the irregular form of the torso will affect the shape and amplitude of the potentials recorded.[17–19] Lewis and Rothschild were the first to recognise that unipolar electrograms contained both local components (intrinsic deflection) and signals generated by more remote tissue (extrinsic deflection).[4]

Later studies have shown that the shapes and peak to peak voltages of unipolar electrograms are influenced mainly by the superposition effects of distant excitation waves and not by local events.[20 21] Blanchard *et al* have shown that the electrical activity associated with activation of the left ventricle has a significant effect on the right ventricular unipolar electrogram even after the two ventricles have been disconnected electrically by a disarticulation procedure.[22] The differences in the durations of the evoked QRS complexes for the bipolar and unipolar packed evoked responses reported in our study are similar to those found in unpaced electrograms,[23] and the longer duration of the unipolar signal indicates that it reflects ventricular activation and repolarisation over a wider area.

The preliminary evidence that the unipolar evoked response might reflect a dominance of local electrophysiological changes around the stimulating electrode was based largely on the finding that the interval between the pacing spike and the apex of the evoked T wave coincided roughly with the time to 90% repolarisation of a locally recorded monophasic action potential. Furthermore, the application of physiological and pharmacological stimuli known to affect the duration of the monophasic action potential caused a parallel change in the duration of the interval from stimulus to apex of the evoked T wave. As the T wave represents the summation at the body surface of the electrical forces during repolarisation, however, any induced changes in the monophasic action potential might be expected to result in similar changes in the T wave.[24 25] Indeed, evidence for this has been reported.[26]

The results of this study are consistent with other comparisons of unipolar and bipolar electrograms, although only limited information is avilable concerning the electrical characteristics of the unipolar paced evoked response.[27] The longer duration of the QRS and QT intervals of the unipolar signal and its closer approximation to the surface electrocardiogram than to the bipolar paced evoked response support the hypothesis that the unipolar evoked response has a significant signal content from more distal portions of the heart, probably including contralateral ventricular electrical activity.[28–30] A bipolar sensing system selectively cancels far field signals and therefore is more likely to represent local depolarisation and repolarisation, and the bipolar ventricular paced evoked response might become more widely used as a measure of local cardiac electrical phenomena.

This is the first study that compares the morphologies and durations of the bipolar and unipolar ventricular paced evoked responses. Our results indicate that, contrary to previously published data, the unipolar paced evoked response is significantly influenced by far field electrical phenomena and is unlikely to give quantitative information about local myocardial depolarisation and repolarisation; these three electrograms should therefore be considered as separate entities. Further studies of the duration of local action potentials that use the paced evoked response are probably best conducted with a bipolar sensing configuration. The larger amplitude of the unipolar paced evoked T wave compared with the simultaneous bipolar signal, however, implies that its detection in the QT sensing pacemaker is more certain with the first sensing configuration.

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Br Heart J 1992;68:403–7

Effects of abnormal activation on the time course of the left ventricular pressure pulse in dilated cardiomyopathy

Han B Xiao, Stephen J D Brecker, Derek G Gibson

Abstract

Objective—**To investigate the effects of QRS duration on characteristics of the left ventricular pressure pulse derived from the time course of functional mitral regurgitation by continuous wave Doppler.**

Design—**Retrospective and prospective study of 50 patients with dilated cardiomyopathy, by electrocardiography, echocardiography, and Doppler cardiography.**

Setting—**Tertiary cardiac referral centre.**

Patients—**50 patients (mean age (SD) 58 (16)) with dilated cardiomyopathy, all with functional mitral regurgitation.**

Results—**The values of QRS duration ranged widely, from 70 to 190 ms with a mean value of 110 ms, and were unimodally distributed. The overall duration of mitral regurgitation correlated positively with QRS time ($r=0{\cdot}65$) over the entire range of values. When the duration of mitral regurgitation was divided into contraction, aortic ejection, and relaxation times, increased QRS duration prolonged contraction ($r=0{\cdot}51$) and relaxation ($r=0{\cdot}52$) times. Aortic ejection time was affected by RR interval ($r=0{\cdot}74$). Duration of QRS correlated negatively with peak rate of rise in left ventricular pressure (+dP/dt) ($r=-0{\cdot}48$), and positively with the time intervals from Q to peak pressure ($r=0{\cdot}49$) and to peak +dP/dt ($r=0{\cdot}72$), and also with those from the start of mitral regurgitation to peak pressure ($r=0{\cdot}49$) and to peak +dP/dt ($r=0{\cdot}76$). Duration of QRS did not directly affect the peak rate of left ventricular pressure fall (−dP/dt), or the isovolumic relaxation period.**

Conclusions—**Values of QRS duration are unimodally distributed in patients with dilated cardiomyopathy, without evidence of a discrete group of patients with left bundle branch block. Prolonged QRS duration reduces peak +dP/dt, prolongs overall duration of the pressure pulse, the time to peak + dP/dt, and relaxation time. Duration of QRS must therefore be taken into account in assessing standard measurements of myocardial function in patients with dilated cardiomyopathy.**

(Br Heart J 1992;68:403–7)

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In 1926, Wiggers[1] questioned whether changes in ventricular conduction were important in determining the dynamics of ventricular contraction. He concluded that intraventricular pressure curves could only be regarded as reflecting the contraction of the individual muscle units of the ventricle as long as excitation passed over natural pathways from a supraventricular focus. Since then, the question has been investigated little, particularly as it applies clinically, and yet it remains an important one. In human left ventricular disease, major disturbances of ventricular activation may occur, yet changes in the pressure pulse are often used to assess myocardial function.[2 3] Peak rate of the rise of pressure standardised to instantaneous pressure has been suggested as an index of contractility, and more recently, the characteristics of the fall of pressure have been widely used to assess relaxation.[3] In our study, we aimed to investigate this problem in a homogeneous group of patients with dilated cardiomyopathy. We assessed the disturbance of activation from QRS duration, computed from the surface electrocardiogram, rather than from the usual electrocardiographic criteria of bundle branch block. We correlated the results with the characteristics of the left ventricular pressure pulse, determined non-invasively by continuous wave Doppler from the time course of functional mitral regurgitation.

Patients and methods

PATIENTS

We studied 50 patients with dilatation of the left ventricular cavity (end diastolic dimension ≥6·5 cm) and reduced shortening fraction (≤15%), aged from 16 to 78 (mean (SD) 58 (16)) years. Five had underlying coronary artery disease and four had had an aortic valve replacement. Patients with hypertension, organic mitral valvlar disease, left ventricular aneurysm, or right bundle branch block were excluded. Twelve patients were in atrial fibrillation, and the remainder were in sinus rhythm. Functional mitral regurgitation was recorded in all.

ELECTROCARDIOGRAPHY

Standard 12 lead electrocardiograms were recorded at a paper speed of 50 mm/s with Hewlett Packard Pagewriter XLi equipment. Computed values of QRS duration, PR interval, and QRS axis were recorded. The method of assessing QRS duration was checked against manual measurements; the mean difference between the two was 1(6) ms.

ECHOCARDIOGRAPHY

M mode echocardiograms guided from the cross sectional display were recorded with the patients in left lateral position, by a 3·0 MHz mechanical transducer with an ATL Mark III system or 2·5 MHz phased array transducer with a Hewlett Packard Sonos 500 system. They were recorded photographically with simultaneous electrocardiograms and phonocardiograms at a paper speed of 10 cm/s. The left ventricular M mode echogram was taken at the tips of mitral leaflets, and end diastolic and systolic dimensions were taken corresponding to the start of the QRS complex and that of the first high frequency vibration of the aortic component of the second heart sound (A_2) respectively. Shortening fraction was then derived in the usual way. Aortic ejection time was measured directly from the aortic echogram, which was also used to identify the aortic component of the second heart sound. Reversed splitting was common in patients with QRS prolongation. Mitral valve opening was taken as the point of initial mitral cusp separation. Isovolumic relaxation time was measured as the interval from A_2 to mitral opening.

Doppler traces were recorded with a 2 MHz pencil transducer and Doptek equipment, again with simultaneous electrocardiogram and phonocardiogram at a paper speed of 10 cm/s. Functional mitral regurgitation in each patient was recorded with continuous wave mode, with a 650 or 1000 Hz filter, from which the following measurements were made[4]:

(*1*) RR interval.

(*2*) The overall duration of mitral regurgitation.

(*3*) Left ventricular contraction time, from the start of mitral regurgitation to the opening of the aortic valve.

(*4*) Aortic ejection time, from the opening of the aortic valve to its closure (A_2).

(*5*) Left ventricular relaxation time, from A_2 to the end of mitral regurgitation.

We digitised the mitral regurgitation signal with time and velocity calibrations, and thus, by means of the modified Bernouilli equation, derived the time course of the pressure drop from the left ventricle to the left atrium along with its rate of change (fig 1). From these plots, we measured:

(*1*) Peak pressure drop from left ventricle to left atrium.

(*2*) Peak rate of pressure rise (+dP/dt) and fall (−dP/dt).

(*3*) The times to peak +dP/dt, with the start of QRS complex and mitral regurgitation as zero.

(*4*) The time interval from A_2 to peak negative dP/dt.

(*5*) The time interval from peak negative dP/dt until mitral valve opening (isovolumic relaxation time minus A_2 to peak −dP/dt).

(*6*) Time to peak pressure—that is, when the dP/dt curve returned to the base line.

DATA ANALYSIS

The mean value of the measurements was obtained from three successive beats and is expressed as mean (SD). The distribution of values of QRS duration within the sample was analysed by a method of normal probability plot.[5] Differences between mean values were assessed by Student's *t* test and linear correlation was performed by the method of least squares. Stepwide regression and χ^2 analyses were also performed as appropriate.

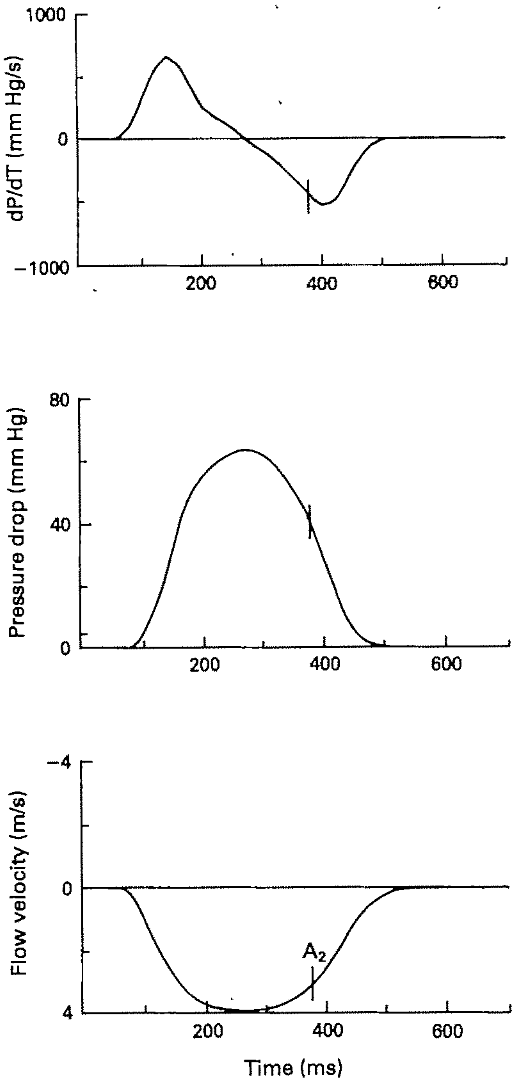

Figure 1 Doppler trace of functional mitral regurgitation (bottom trace) with calculated pressure drop (middle trace) and its first derivative (top trace). Zero time represents the start of QRS complex, A_2 represents the time of aortic closure.

Results

Table 1 gives general electromechanical measurements.

QRS DURATION

The values of QRS duration in individual patients ranged widely, from 70 to 190 ms with a mean value of 110 ms. With a normal probability plot method,[5] the distribution (r = 0·984) did not differ significantly from normal (r = 0·976, α=0·05). Left axis deviation was present in patients with normal QRS complexes, though it was commoner in patients with broad QRS complexes (fig 2). Although many of those with a QRS duration of 120 ms or more had features suggestive of left bundle branch block, we treated QRS duration as a

Table 1 Electromechanical measurements

Index	*Value mean (SD)*
Age (y)	58 (16)
Left ventricular end diastolic dimension (cm)	6·9 (0·9)
Shortening fraction (%)	11 (1·5)
RR interval (ms)	725 (195)
PR interval (ms)	175 (35)
QRS duration (ms)	110 (30)
QRS axis (degrees)	16 (50)
Overall duration of mitral regurgitation (ms)	415 (80)
Pre-ejection contraction time (ms)	80 (30)
Aortic ejection time (ms)	245 (45)
Left ventricular relaxation time (ms)	90 (30)
Peak pressure difference (mm Hg)	70 (30)
Q to peak pressure difference (ms)	235 (45)
Q to peak +dP/dt (ms)	115 (30)
Start of mitral regurgitation to peak +dP/dt (ms)	50 (35)
Isovolumic relaxation time (ms)	45 (25)
Peak +dP/dt (mm Hg/s)	690 (205)
A_2 to peak −dP/dt (ms)	10 (25)
Peak −dP/dt to mitral opening (ms)	30 (25)
Peak −dP/dt (mm Hg/s)	600 (220)

+dP/dt, Peak rate of pressure rise; −dP/dt, peak rate of pressure fall.

single continuous variable and did not attempt to identify electrocardiographic patterns associated with pathological Q waves or with block of one or more of the fasicles of the left bundle.

EFFECT OF QRS DURATION ON MITRAL REGURGITATION

Table 2 shows the overall duration of mitral regurgitation correlated positively with QRS time ($r = 0{\cdot}65$) over the whole range of values studied. The slope of the relation, 1·7, was significantly greater than 1.

When the duration of mitral regurgitation was divided into contraction, aortic ejection, and relaxation times, increased QRS duration increased contraction ($r = 0{\cdot}51$) and relaxation ($r = 0{\cdot}52$) times. The RR interval was the only other factor affecting the duration of mitral regurgitation on stepwise regression analysis, which was performed with PR interval, QRS duration, age, and left ventricular size as additional independent variables. The effect of RR interval was mediated mainly by its exclusive influence on aortic ejection time ($r = 0{\cdot}74$), and by a small, additional effect on relaxation time (table 3).

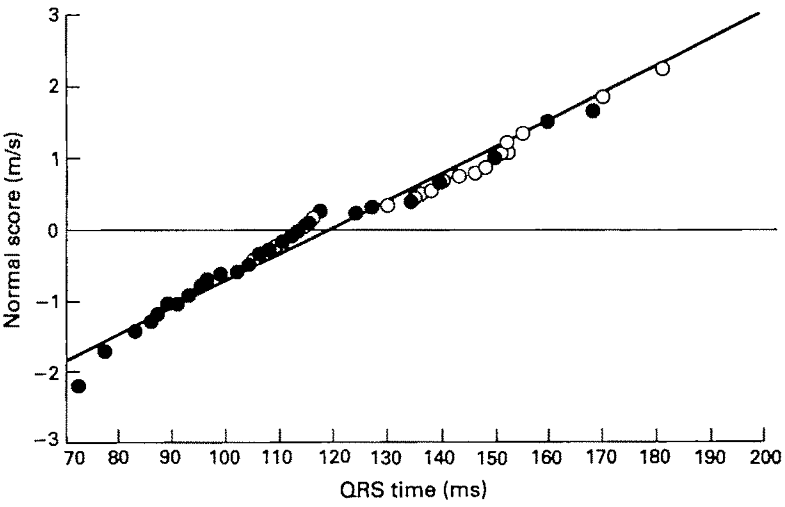

Figure 2 Normal distribution plot of QRS duration. Open symbols represent patients with left axis deviation and closed symbols those without. Note that QRS duration itself is unimodally distributed throughout the sample studied although left axis deviation is commoner when QRS duration is prolonged.

EFFECT OF QRS DURATION ON DERIVED LEFT VENTRICULAR PRESSURE CURVE

The QRS duration correlated negatively with peak rate of rise in left ventricular pressure (+dP/dt) ($r = -0{\cdot}48$), and positively with the time intervals from Q to peak pressure ($r = 0{\cdot}49$), to peak +dP/dt ($r = 0{\cdot}72$), from the start of mitral regurgitation to peak pressure ($r = 0{\cdot}49$), and to peak +dP/dt ($r = 0{\cdot}76$). Thus when QRS duration increased, the time to peak rate of rise in pressure was prolonged and the maximal rate of the rise in pressure fell. Duration of QRS was the dominant factor influencing the times to peak +dP/dt ($r^2 = 52\%$ and 62%, respectively). Duration of QRS, however, did not directly affect the peak rate of fall of left ventricular pressure (−dP/dt), or the isovolumic relaxation period.

Discussion

Dilatation of the left ventricular cavity with reduced ejection fraction is widely attributed to severe myocardial disease, and the impaired systolic performance explained on the basis of reduced contractility.[2] Although there is no general agreement as to how this term is defined or even whether the entity exists at all, at least one approach to measuring it, V_{max}, has been based on estimating rates of development of myocardial stress.[2] Similarly, abnormal relaxation has been diagnosed on the basis of reduced rate of fall of pressure, measured by a time constant.[3] These methods both assume that, in Wiggers' terminology, the properties of the fractional units of myocardium can be deduced directly from the properties of the ventricular pressure pulse. Wiggers' work suggested that this was only possible when activation was normal. Increased dispersion in the time of the start of activation in different regions of the ventricle may itself cause corresponding asynchrony in regional mechanical properties of the ventricle. This will reduce rates of rise and fall of ventricular pressure independently of any intrinsic myocardial disease. It was this question that we aimed to answer in our study. We chose a homogeneous group of patients with increased cavity size and reduced shortening fraction. We took advantage of recent studies indicating that when mitral regurgitation is functional and mild, the time course of the left atrium to ventricle pressure difference closely follows that of the intraventricular high fidelity pressure trace.[6–8] This non-invasive approach made it possible to study a large series of patients with a wide range of QRS duration.

In the absence of rightwardly directed terminal forces, a broad QRS complex is usually described as left bundle branch block.[9] This is a useful clinical term based on simple electrocardiographic pattern recognition, which identifies a group of patients with a major disturbance of activation. We used this approach in a recent study to show that when left bundle branch block was present it was associated with

Table 2 Correlation of QRS duration (ms) with other measurements

	Slope	*(SEM) slope*	*Intercept*	*(SEM) intercept*	*r Value*
Overall MR duration (ms)	1·7	(0·28)	230	(33)	0·65
Contraction time (ms)	0·45	(0·11)	28	(12)	0·51
Aortic ejection time (ms)	0·42	(0·19)	200	(23)	0·29
Relaxation time (ms)	0·49	(0·12)	33	(14)	0·52
Q to peak +dP/dt (ms)	0·61	(0·11)	48	(13)	0·72
Start of MR to peak +dP/dt (ms)	0·69	(0·11)	−27	(13)	0·76
Peak +dP/dt (mm Hg/s)	−3 0	(1·01)	1040	(120)	−0·48
Q to peak pressure (ms)	0·67	(0·21)	160	(25)	0·49
Start of MR to peak pressure (ms)	0·77	(0·24)	83	(29)	0·49

MR, mitral regurgitation.

prolonged systolic activity and consequent shortening of left ventricular filling time.[4] Objective analysis of QRS, however, shows not only considerable variation within patients classified as having left bundle branch block, but also in patients in whom the electrocardiographic criteria do not apply. In our study, based on a separate group of patients, we have used commercially available software to compute QRS duration, rather than the classical electrocardiographic criteria. It has shown that in patients with dilated cardiomyopathy, QRS duration is effectively unimodally distributed rather than being segregated into two groups with and without left bundle branch block. This finding obviously raises questions of definition as well as providing further evidence that the prolonged QRS duration in patients with dilated cardiomyopathy is due to an arborisation block, probably diffusely affecting the whole ventricle.[4]

It was possible, with echocardiography, phonocardiography and Doppler, to define a series of associations between QRS duration and the time course of the functional mitral regurgitation and thus of the pressure difference between left ventricle and atrium. Not surprisingly, the stronger correlations of QRS duration were with events early in systole—in particular the time interval from the Q wave and from the start of pressure rise to peak +dP/dt and to a lesser extent with +dP/dt itself. The overall duration of mitral regurgitation, however, and the relaxation time (A_2 to the end of mitral regurgitation) also correlated significantly with QRS duration, accounting for 25% or more of the total variance ($r^2 = 0{\cdot}27$). Duration of QRS correlated only weakly with ejection time and not at all with peak negative dP/dt. We noted that mitral valve cusp separation followed the time of peak −dP/dt by a mean value of 30 ms, and sometimes even preceded it. We have previously shown that mitral regurgitation may continue for up to 100 ms after mitral cusp separation in these patients.[10] This has remained a consistent finding which we are unable to explain, but which seems to warn of complex and poorly understood factors operating at this stage in the cardiac cycle. We have thus hesitated to calculate time constants of relaxation from the Doppler derived pressure curve in our patients, particularly in the light of increasing experimental evidence suggesting that even in the normal heart, the time course of the fall in left ventricular pressure is not exponential.[11]

Table 3 Determinants of systolic and diastolic time intervals (ms) (stepwise regression analysis)

Index	*Intercept*	*Slope*		*Multiple correlation coefficient*
		QRS	*RR*	
Mitral regurgitation time	96	1·31	0·24	0·85
Filling time	−36	−1·47	0·71	0·93
Contraction time	18	0·55	NS	0·54
Ejection time	112	NS	0 17	0·74
Relaxation time	−2	0·40	0·06	0·64

NS, coefficient not significantly different from zero.

To predict the effects of activation on the pressure pulse, Wiggers developed a simple model based on algebraic summation of the contraction of the subunits.[1] It suggested that increasing the period over which the summation occurs, the equivalent of prolonging the QRS duration, should not alter the time of the start of the rise in pressure, although peak rate of rise and fall would be reduced. The time intervals to peak rate of rise and peak pressure would be prolonged as would be the overall duration of the pressure pulse, each by the same amount as the increase in QRS duration, although peak pressure itself is unlikely to be changed. Our findings thus agree closely with these predictions especially with respect to early systole and the overall duration of mitral regurgitation. The main points of difference were the lack of correlation of −dP/dt with QRS duration, although relaxation time itself correlated, and also that the extent of the prolongation of mitral regurgitation was 70% greater than that of the QRS complex itself. In general, therefore, observation agrees with prediction enough to suggest that the electromechanical correlations we describe could be explained largely on the basis of the theory of fractionate contractions.

Our results may have some practical significance especially when it comes to assessing myocardial function. Peak dP/dt, or peak dP/dt standardised to instantaneous pressure, are still recommended as being of value in assessing myocardial systolic performance and described as contractility.[12 13] Clearly such estimates depend critically on the pattern of ventricular activation. This was not allowed for in the original studies, an omission that may contribute to the poor performance of such isovolumic indices in identifying patients with reduced systolic function. Also, acute change in dP/dt, dP/dt standardised to instantaneous pressure, or time to peak dP/dt are often used to assess the effect of drugs. Should the drug also prolong QRS duration, then effects on the pressure curve would be expected as the direct consequence of the electrophysiological change and need not be attributed to depressed function of individual myocardial units.[14 15]

In summary, therefore, our resuts show the potential value of taking QRS duration into account in assessing both systolic and diastolic myocardial function, in patients with dilated cardiomyopathy. The QRS duration is routinely computed and printed out by modern electrocardiographs; such values are little used clinically, but are clearly significant once their consequences in terms of the severity of the haemodynamic disturbance in individual patients are considered. Further, if QRS duration could be reduced, possibly by an appropriate pacing technique, the equivalent of a positive inotropic effect on rates of both contraction and relaxation could be achieved without the complications of tachyphylaxis, increasing myocardial oxygen requirements, or a proarrhythmic effect. We feel that these electromechanical interactions are worthy of study.

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CASE REPORTS

Mitochondrial DNA deletion diagnosed by analysis of an endomyocardial biopsy specimen from a patient with Kearns-Sayre syndrome and complete heart block

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Abstract

Defects of mitochondrial DNA have been found at necropsy in the myocardium of patients with Kearns-Sayre syndrome. A patient with characteristics typical of Kearns-Sayre syndrome and a complete heart block is described. Southern blot analysis showed a deletion of 3·3 kb in the mitochondrial DNA in an endomyocardial biopsy specimen and in skeletal muscle. The deletion led to the disappearance of the genes for four transfer RNAs and four subunits of complex I (NADH:ubiquinone oxidoreductase) in the mitochondrial respiratory chain. The defect could not be demonstrated in whole blood despite amplification of the mitochondrial DNA region of interest by the polymerase chain reaction technique. There can be heteroplasmy—that is, normal and abnormal mitochondrial DNA populations in one cell—in different tissues, and the degree of heteroplasmy may be crucial in the development of organ-specific symptoms. This patient raises the possibility that some tissues can be specifically enriched with mitochondria with DNA defects and emphasises the need for elective sampling of the target tissue and polymerase chain reaction technique to exclude these defects. The role of mitochondrial DNA defects in idiopathic cardiomyopathies could perhaps be studied by analysis of mitochondrial DNA from endomyocardial biopsy specimens.

(*Br Heart J* 1992;68:408–11)

Kearns-Sayre syndrome is characterised by onset before age 20, progressive external ophthalmoplegia, and abnormal retinal pigmentation. In addition, diagnosis depends on at least one of the following signs being present: complete heart block, cerebellar dysfunction, or high cerebrospinal fluid protein.[1] The syndrome belongs to the category of mitochondriopathies with defects in mitochondrial DNA[2] and it has been suggested that selective involvement of the cardiac conduction system leads to conduction abnormalities.[3–5] A patient with the typical characteristics of Kearns-Sayre syndrome and rapid development of congestive heart failure who required heart transplantation has been reported, however.[6]

Mitochondrial DNA is a small (16·5 kb), circular, double stranded molecule that contains 13 genes for peptides of the mitochondrial respiratory chain, 12 transfer RNA genes, and two genes encoding mitochondrial ribosomal RNAs.[2] The diagnosis of cardiac involvement in mitochondriopathies has relied on typical electrocardiographic changes and ultrastructural findings in an endomyocardial biopsy specimen[7] or the analysis of mitochondrial DNA in hearts at necropsy.[8 9] We describe a patient presenting with a complete heart block and clinical features of Kearns-Sayre syndrome, in whom the mitochondrial DNA defect was characterised and its distribution in various tissues studied.

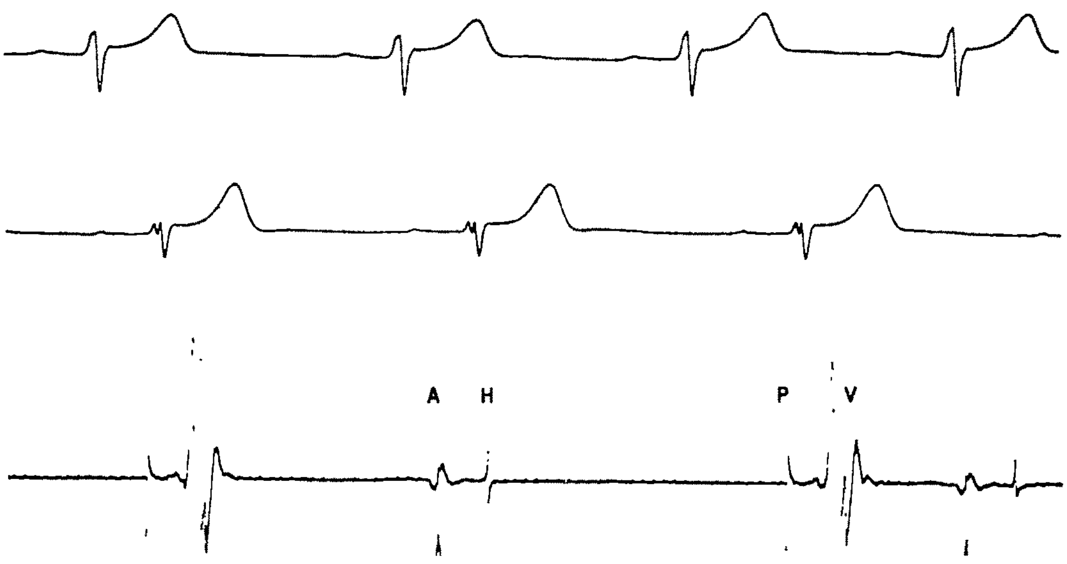
Case report

The patient had an uneventful childhood, but noticed weakness of the eyelids at the age of 17; one year later bilateral ptosis was seen. Retinal degeneration and decreased visual acuity were also diagnosed, but ocular movements were intact. A neurological examination at the age of 18 showed myopathic facies, diffuse slowing in the electroencephalogram, normal cerebrospinal fluid protein (330 mg/l), and a normal electromyogram. Symmetrical hearing loss was continued at the age of 19 and ocular movements were restricted in all directions at 21. Several operations were performed later for bilateral ptosis, and in his 30's he began to experience muscle weakness during exercise, although he was still able to work on the family farm.

The patient had no cardiac symptoms until he collapsed on two occasions at the age of 38, whereupon a complete electrocardiographic heart block was diagnosed. An electrophysiological examination showed a block in the conduction system distal to the His bundle (fig 1), and a DDD pacemaker was implanted. Echocardiography was normal.

A neurological examination showed a general decrease in muscle mass and specifically muscle atrophy and weakness of the facio-

Figure 1 Electrocardiogram showing conduction block distal to His bundle. Upper and middle tracings are lead V2 in 1981 and 1982 respectively. Lower tracing is His electrocardiogram in 1991. A, atrial deflection; H, His potential; P, pacemaker artefact; V, ventricular complex.



scapulohumeral type. There was a complete external ophthalmoplegy, moderate bilateral ptosis and pigmentary retinopathy. Tendon reflexes, sensation, and coordination were normal. The electroencephalogram was diffusely abnormal, with theta activity. Computed brain tomography showed cortical atrophy. Nerve conduction velocities were normal but the electromyogram showed changes consistent with mild myopathy. There was a symmetrical sensorineural hearing loss. He was considered to be of average intelligence.

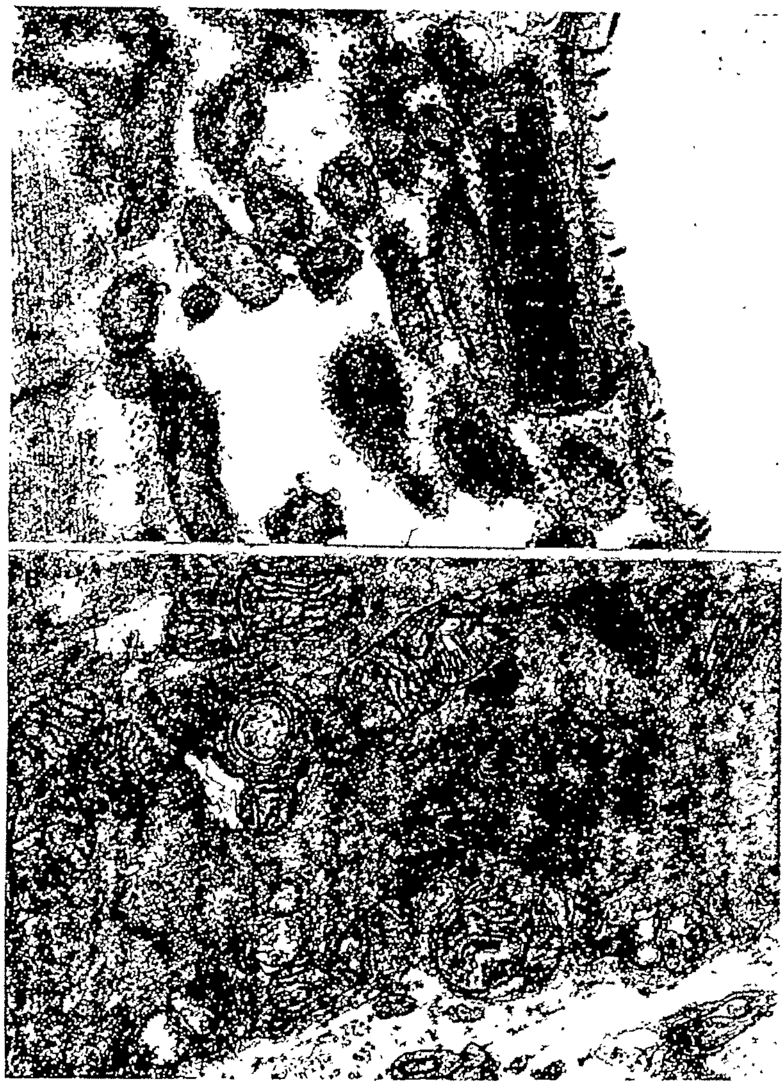


Figure 2 (A) Electron micrograph of skeletal muscle showing abnormal mitochondria with paracrystalline inclusions and a concentric arrangement of the cristae.
(B) Electron micrograph of endomyocardium showing prominent accumulations of mitochondria, some of which showed concentric cristae.

There were no abnormalities in routine laboratory tests and no raised titres of antibodies to any micro-organism were detected. Antinuclear antibodies (IgG) were somewhat raised as was the resting blood pyruvate concentration (115 μmol/l, normal range 45–85). The resting lactate concentration varied from 1·31 to 2·80 mmol/l (normal range 1·0–1·8), and during a forearm ischaemic exercise test lasting two minutes (five-fold increase normal) increased 7·5 fold from the baseline value. The urine aminoacid analysis was normal.

Several endomyocardial biopsy specimens and a skeletal muscle biopsy specimen were taken for histopathological examination and mitochondrial DNA analysis. Light microscopy after Gomori trichrome staining of the skeletal muscle showed scattered ragged red fibres but otherwise the muscle was normal. Electron microscopy study showed abnormal mitochondria with paracrystalline inclusions and a concentric arrangement of the cristae (fig 2A). The endomyocardium was normal by light microscopy, but electron microscopy showed prominent accumulations of mitochondria, some of which showed abnormal concentric cristae (fig 2B).

The activities of the mitochondrial respiratory chain enzymes were analysed by oximetry and spectrophotometric methods applied to mitochondria isolated from the skeletal muscle. The activities of the enzymes were normal when studied by oximetry, but spectrophotometry showed a decrease in NADH-cytochrome *c* reductase activity (42 nmol/min/mg protein, normal range 63–230). Total DNA was isolated from frozen endomyocardial and skeletal muscle biopsy specimens and whole blood by the standard phenol/chloroform/isoamyalcohol method. 1 μg of DNA was digested with the restriction enzyme Pvu II, which cuts the mitochondrial

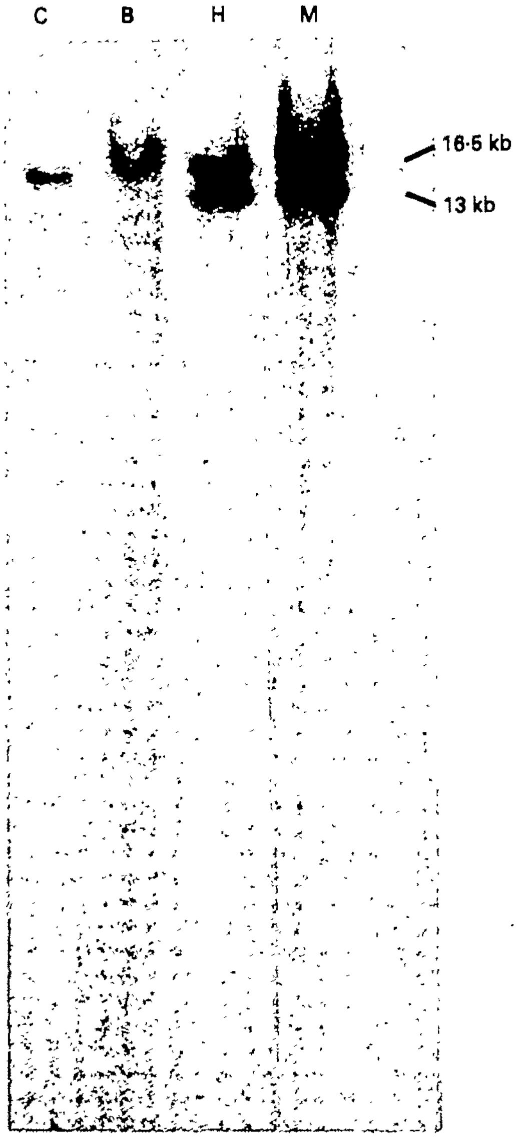


Figure 3 *Southern blot analysis of blood (B), heart (H), and skeletal muscle (M) from a patient with Kearns-Sayre syndrome. C, control.*

DNA molecule at only one site and produces a single 16·5 kb linear molecule. Polymorphism for this restriction enzyme is extremely rare. The digests were separated electrophoretically in 0·8% agarose gel and transferred to nitrocellulose. The filters were hybridised with a whole mitochondrial DNA probe isolated from human placenta and radiolabelled by the random primer method. Southern blot analysis of heart and skeletal muscle (but not blood) showed two populations of mitochondrial DNA, one corresponding to full-length molecules of mitochondrial DNA and the other, which migrated more rapidly in the electrophoretic gel, corresponding to a smaller mitochondrial DNA (fig 3). The deleted portion of the mtDNA was roughly located by analysis for the absence of known restriction sites.[2] After mapping, the polymerase chain reaction technique was used for selective amplification of the region spanning the deleted mitochondrial DNA. The same method did not detect any deletion in whole blood mitochondrial DNA. Direct sequencing of the amplified product showed a 3·3 kb deletion (map position 10169-13406 in the Cambridge sequence). The deleted region included four transfer RNAs (Arg, His, Ser, Leu) and four subunits of Complex I of the mitochondrial respiratory chain.

Discussion

The cardiac abnormalities associated with the Kearns-Sayre syndrome have been considered to be limited to the conduction system. The most common conduction abnormality is left anterior hemiblock, alone or in combination with a right bundle branch block; while others include Mobitz type II second degree atrioventricular and complete heart block.[4-6] Progressive impairment of infranodal conduction is typical of these patients, but, somewhat paradoxically, increased velocity of atrioventricular nodal conduction has also been seen.[4] Because of the progressive nature of the conduction abnormality and the increased life-threatening risk associated with high-degree infranodal heart block, prophylactic pacemaker treatment has been recommended for these patients.[4 10] It is important to differentiate between Kearns-Sayre patients and patients having left axis deviation in combination with a right bundle branch block without myocardial infarction, because the latter do not generally require pacemaker therapy.[11]

Our patient presented with a complete heart block. Two earlier electrocardiograms were available (10 and nine years old). The older one was apparently normal, but the nine year old electrocardiogram showed some prolongation of the PR interval and signs of impairment of intraventricular conduction, confirming the progressive nature of the conduction abnormality. The electrophysiological examination showed that the block was infranodal and distal to the His bundle (fig 1).

Proliferation of mitochondria between the myofibrils and sarcolemma was found in electron micrographs of the myocardial biopsy specimen, with many of the mitochondria showing curved cristae and vacuolisation (fig 2). These features are typical of the Kearns-Sayre syndrome.[10]

The fact that a patient with Kearns-Sayre syndrome developed congestive heart failure requiring transplantation[6] suggests that the defect in mitochondrial DNA is not necessarily limited to the conduction system. The mitochondrial DNA deletion of 3·3 kb found in the present case leads to defective synthesis of four transfer RNAs and four subunits of Complex I in the mitochondrial respiratory chain, which should impair oxidative energy transfer. Mechanical function, as assessed by echocardiography, was perfectly normal, however. This finding also accords with measured mitochondrial enzyme activities and points to the fact that a considerable proportion of the heteroplasmic mitochondrial population is normal. It may also be that the cardiomyocytes are more resistant to the metabolic abnormality associated with the mitochondrial DNA defects than are the cells of the conduction system or that the conduction system is enriched with mitochondria with DNA deletions. On the other hand, the amount of deleted mitochondrial DNA in different tissues and organs—that is, the degree of heteroplasmy—may determine the final manifestations of the syndrome.[12]

It has been recognised that diseases related to defects in mitochondrial DNA may be tissue specific, and the dogma of identical mitochondrial DNA in all the cells of an individual no longer holds true. This was also apparent in our patient, in whom heteroplasmy was shown in the tissues related to the symptoms but not in the leucocytes or platelets, for example. A skeletal muscle biopsy may therefore not be sufficient to diagnose or exclude cardiomyopathy caused by defective mitochondrial DNA.

Deletion of mitochondrial DNA is commonly detected in elderly subjects, the proportion of the deleted species increasing with age. Moreover, it has been suggested that accumulation of this deletion may contribute to the ageing process and the occurrence of presbycardia.[13]

It has been thought that the aetiology of dilated cardiomyopathy is related to autoimmunity, suggesting that a predisposition towards it may be determinated by the major histocompatibility complex genes,[14] but a viral aetiology has also been reported.[15] It may well be that dilated cardiomyopathy is multifactorial in origin, as some cases of isolated cardiomyopathy have been recently described in which there were multiple mitochondrial DNA deletions or point mutations.[8 16 17] This emphasises the role of organ-specific sampling and analysis of mitochondrial DNA. A prospective study to search for mitochondrial DNA defects may help to clarify the role of these genetic defects—for example, in patients with dilated cardiomyopathy.

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Br Heart J 1992;**68**:412–3

Apparent obstruction of the superior vena cava and a continuous murmur: signs of a fistula between a vein graft aneurysm and the right atrium

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Abstract

A previously undescribed complication of a saphenous vein aortocoronary bypass graft, namely formation of a fistula between a vein graft aneurysm and the right atrium is reported. A patient presented with a continuous murmur and a combination of signs suggesting superior vena cava obstruction. This pathology was shown by both echocardiography and angiography. Surgical treatment was attempted.

(*Br Heart J* 1992;**68**:412–3)

Aneurysms of saphenous vein grafts, first recognised in 1975, are now a well recognised complication of coronary artery bypass surgery.[1] Such aneurysms may be further complicated by thromboemboli causing ischaemia,[2] myocardial infarction,[3] rupture,[4] or by formation of a fistula to the right ventricle.[5] We report here a case of formation of a fistula between an aortocoronary saphenous vein graft and the right atrium. To our knowledge this has not previously been reported.

Case report

A white man born in 1917 underwent xenograft of the aortic valve and saphenous vein bypass grafting to left anterior descending, circumflex, and right coronary arteries at another hospital in 1980. Subsequently he was free of symptoms for nine years, but had a recurrence of stable, non-limiting angina for two years before his admission to hospital. Two days before admission to hospital he experienced a sudden onset of severe right shoulder and neck pain that worsened steadily. He was breathless. On admission to a local district general hospital his physical signs suggested biventricular failure, and diuretic treatment was started. There was no improvement. Echocardiography showed a right atrial abnormality that prompted immediate referral to the regional cardiac centre.

On arrival at Papworth Hospital the patient was still experiencing severe right shoulder, neck, and back pain. He was confused and clammy. He had a regular, collapsing pulse of 90 per minute, and a blood pressure of 130/60 mm Hg was recorded in both arms. Peripheral pulses were all present, equal, and symmetrical. Particularly striking was the grossly raised venous pressure, with distention of the neck veins and a suffused face. A continuous murmur was noted that was heard loudest at the left and right sternal edges. Bilateral basal crepitations were found but there was no peripheral oedema. Investigations showed a normal full blood count, normal electrolytes, but impaired renal function with 25 mmol/l urea and 330 μmol/l creatinine. The electrocardiogram showed sinus tachycardia with left bundle branch block and left ventricular hypertrophy. A chest radiograph showed right basal shadowing with no evidence of left ventricular failure. Echocardiography showed a circular, doughnut shaped area of high echo density with a diameter of about 4 cm in the region of the right atrium (fig 1). It was unclear what this was and immediate cardiac catheterisation was undertaken.

An aortogram through the right femoral artery showed a normal arch, with no evidence of dissection, or a ruptute of an aneurysm in the sinus of Valsalva. Left ventricular function was good. Contrast was seen in filling the right atrium and the vein graft to the right coronary artery, which was grossly dilated in its mid third (fig 2). A fistula clearly existed between the graft and the right heart cham-

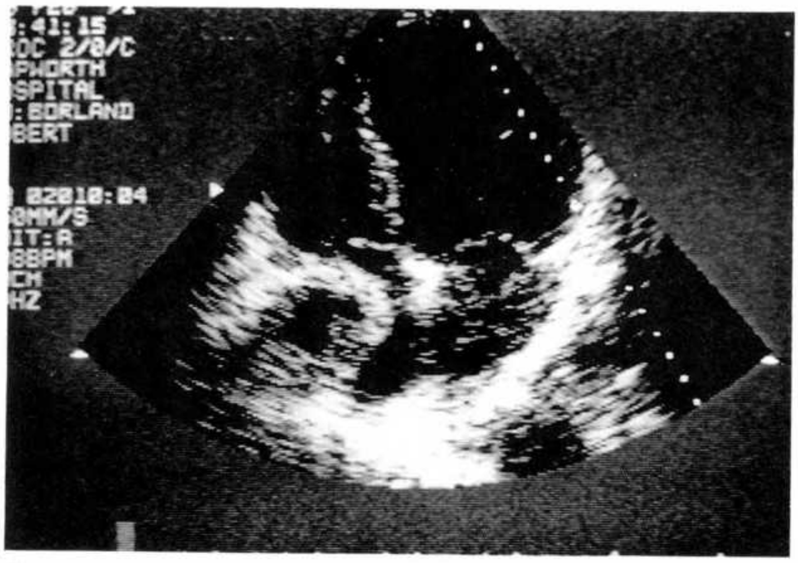

Figure 1 Four chamber transthoracic echocardiogram showing doughnut shaped right atrial abnormality.

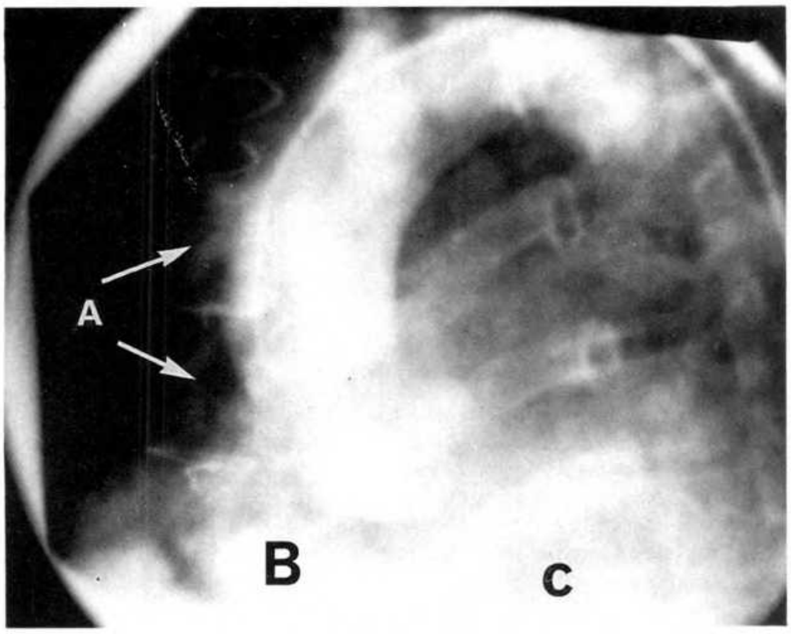

Figure 2 Aortogram in left anterior oblique position showing opacification of the right coronary artery graft (A) with contrast filling the aneurysm (B) and the right atrium (C).

bers, and immediate surgery was undertaken.

The patient was transferred to the operating theatre where electrocardiographic, central venous and arterial pressure monitoring were started. A general anaesthetic was given and median sternotomy was performed. The pericardium was open from previous surgery and there was no free fluid. Arterial and venous cannulation were performed through the left femoral vessels. This allowed cardiopulmonary bypass (CPB) to be established. An atrial venous cannula was connected to the circuit via a Y-shaped connection the venous side and placed in the right atrium once the heart was further dissected.

The previous vein grafts were identified; the graft to the circumflex system appeared as a thin cord with no flow. The graft to the left anterior descending artery was patent. The graft to the right coronary artery was patent but was dilated with an aneurysm in it's midportion, which was densely adherent to the right atrium. During further dissection of the heart, sinus rhythm was lost and difficulties were experienced in maintaining CPB in the absence of an aortic cross clamp. When the right coronary graft was cross clamped, systemic pressures returned and normal bypass was achieved. It was apparent that the aortic return was passing through the right graft, across the fistula to the right atrium and returning directly as venous drainage.

The fistula was excised, the right atrium closed, and the existing right coronary graft ligated proximal to the fistula. There was good back flow from the distal portion of the graft, which was also ligated. Inotropic support was started and weaning from CPB was attempted. Biventricular failure supervened and CPB could not be weaned. The pump was switched off and the patient declared dead.

At postmortem examination it was noted that there was severe atheroma of the aorta and major arteries. The right coronary graft was arterialised with severe ulcerated atheroma. The aneurysm of its midportion was nine cm in circumference and contained old and recent thrombi. The right coronary artery was less occluded distally than the other native vessels. The right atrium was slightly dilated and the right ventricle was both dilated and hypertrophied. The left atrium and ventricle were not dilated and the aortic xenograft undamaged.

Discussion

It is likely that the acute presentation of this case resulted from the acute formation of the fistula from the aneurysm of the right coronary to the right atrium with a resulting significant shunt from aorta to right atrium. Surgery was clearly the only therapeutic option, but this patient's ischaemic myocardium did not function adequately after bypass despite successful repair of the fistula.

The mechanisms responsible for formation of aneurysms in saphenous vein grafts have been suggested to include distension of the vessel wall at the site of venous valves which lack circular muscle,[6] and atheroma.[7] Furthermore, such aneurysms are more common five or more years after surgery and in patients with hyperlipidaemia.[8]

It is notable that this complication was shown by both angiography and echocardiography. Aneurysm of coronary artery vein grafts has previously been shown by transoesophageal echocardiography on one occasion[3] but to our knowledge never by transthoracic echocardiography. Its appearance is highly unusual.

The clinical signs in this patient are unique. His venous pressure was considerably raised with a continuous murmur. In a patient who has had an aortocoronary graft such a murmur has been said to be indicative of the inadvertent anastomosis of the distal end of the graft to a coronary vein.[9] We would like to add to this diagnosis that of a fistula between an aortocoronary graft and the right atrium.

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Br Heart J 1992;68:414–6

A posteroseptal accessory pathway located in a coronary sinus aneurysm: diagnosis and radiofrequency catheter ablation

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Abstract

A coronary sinus aneurysm was diagnosed by means of echocardiography, coronary sinus contrast angiography, coronary angiography, and nuclear magnetic resonance imaging in a patient with Wolff-Parkinson-White syndrome caused by a posteroseptal accessory pathway. Percutaneous radiofrequency current catheter ablation performed in the isthmus of the coronary sinus aneurysm was successful.

(*Br Heart J* 1992;68:414–6)

In recent years curative percutaneous radiofrequency current ablation has been used with great success in patients with Wolff-Parkinson-White syndrome.[1]

In patients with posteroseptal accessory pathways the procedure is often performed by positioning the ablation catheter along the tricuspid annulus near the coronary sinus orifice. There is an association between posteroseptal accessory pathways and coronary sinus aneurysms.[1-3] A coronary sinus aneurysm was found in six (9%) of 65 patients with posteroseptal accessory pathways who underwent surgical ablation.[5] The malformation was also diagnosed at necropsy in patients who died suddenly from cardiac arrhythmias caused by Wolff-Parkinson-White syndrome.[1-3] Most recently, catheter ablation with low energy DC shocks was successful in a patient with a posteroseptal accessory pathway associated with a diverticulum of the coronary sinus.

We report a patient in whom a posteroseptal accessory pathway located in a coronary sinus aneurysm was diagnosed by coronary sinus contrast angiography, coronary angiography, echocardiography, and nuclear magnetic resonance imaging. Radiofrequency currrent applied in the isthmus of the aneurysm successfully ablated the accessory pathway.

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Case report

The patient, a 26 year old man, had had symptoms from the age of eight with attacks of palpitation and dizziness usually evoked by strenuous exercise. Eleven years before his admission Wolff-Parkinson-White syndrome was diagnosed (fig 1).

He was treated with verapamil, flecainide, and then amiodarone without success. Paroxysms with atrial fibrillation and broad irregular QRS complexes and a heart rate of 280–300 beats per minute occurred once or twice a year: usually DC cardioversion was necessary. The patient was referred to us for ablation. An electrophysiological study confirmed the presence of a posteroseptal accessory pathway with both anterograde and retrograde conduction properties. The effective refractory period of the accessory pathway was less than 200 ms. Several times during the study the patient went into atrial fibrillation and had to be cardioverted. The accessory pathway was mapped with a deflectable Mansfield catheter with a 4 mm tip (Mansfield-Webster, Boston Scientific, Watertown, MA, USA), and the shortest atrioventricular and ventriculoatrial intervals as well as a discrete accessory pathway potential were recorded in the coronary sinus 1–2 cm distal from the orifice.

Radiofrequency ablation was attempted with the mapping catheter at several sites along the posterior tricuspid annulus and around the orifice of the coronary sinus without success. Because the failure of the ablation suggested a coronary sinus aneurysm we obtained an angiogram of the left coronary artery and the coronary sinus. This showed a 2 × 3 cm aneurysm of the coronary sinus

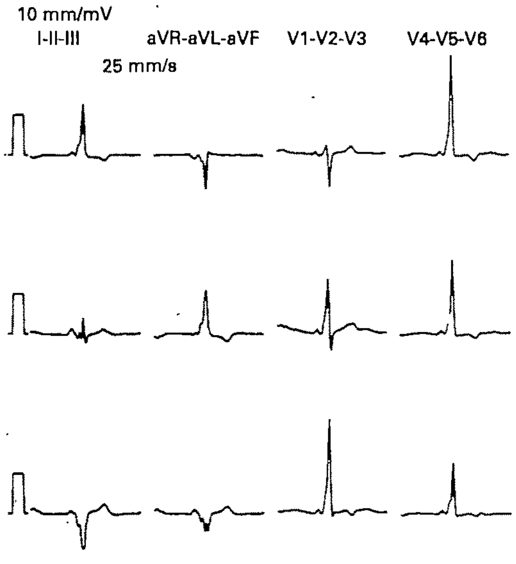

Figure 1 Twelve lead electrocardiogram before radiofrequency ablation showing preexcitation pattern suggesting a posteroseptal accessory pathway.

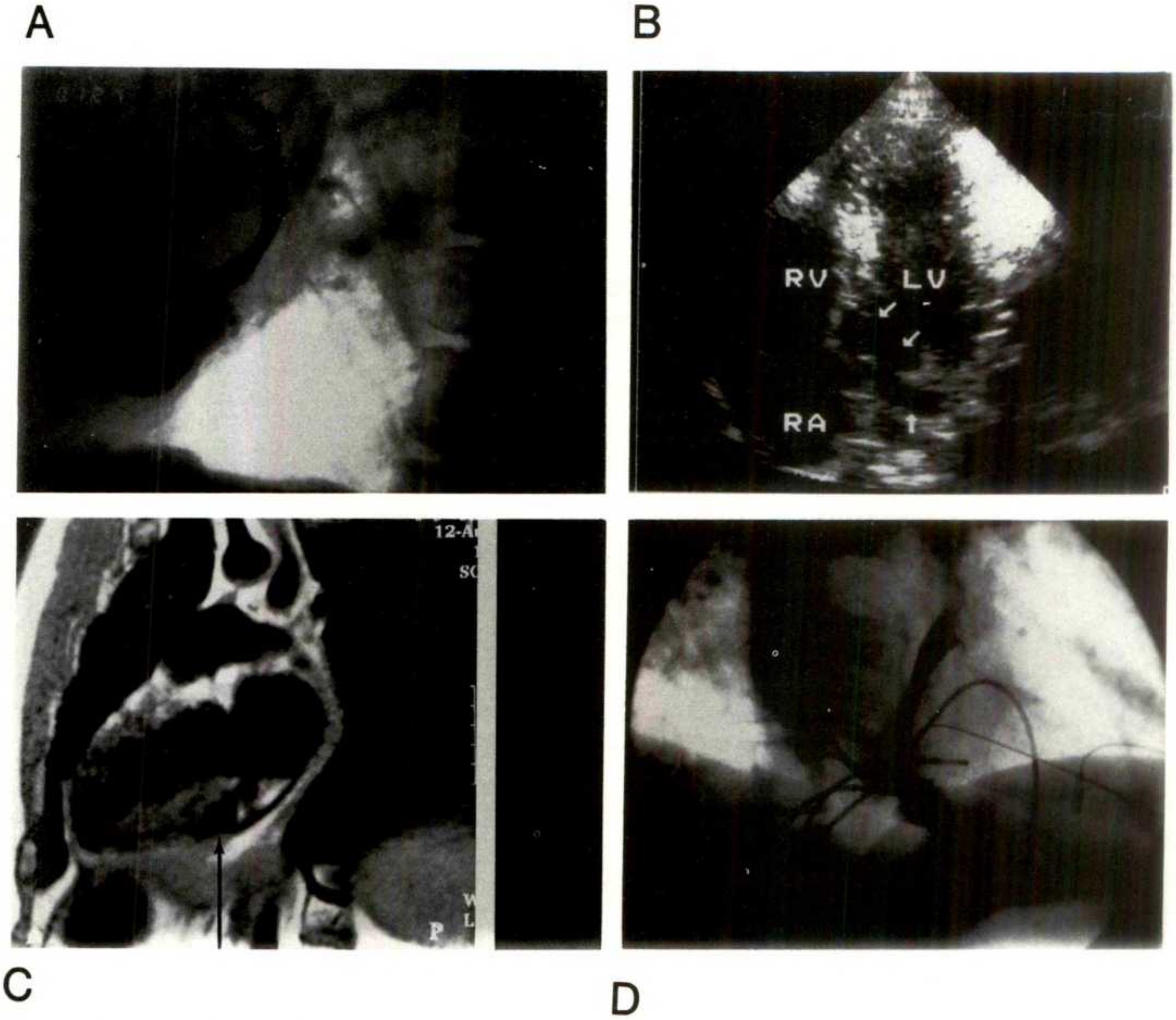

Figure 2 *(A) Coronary sinus angiogram (left anterior oblique projection) showing the coronary sinus and the aneurysm of the coronary sinus with a dividing septum and a narrow isthmus. (B) Cross sectional echocardiogram showing the coronary sinus aneurysm divided by a septum (oblique arrows) and the coronary sinus proper (vertical arrow). LV, left ventricle; RV, right ventricle; RA, right atrium. (C) Nuclear magnetic resonance image of the heart showing the coronary sinus aneurysm with the communication to the coronary sinus proper (arrow). (D) Coronary sinus angiogram (right anterior oblique projection) showing the position of the ablation catheter in the isthmus of the coronary sinus aneurysm. Two standard electrode catheters were placed in the right ventricular apex and on the His bundle respectively.*

with a narrow isthmus and a septum dividing the aneurysm (fig 2A), which extended apically on the inferior surface of the left ventricle along the course of the posterior descending coronary artery. The aneurysm showed contractile systolic movements, almost like a rudimentary ventricle, and it was filled in late diastole from the distal coronary sinus. A standard Doppler echocardiographic examination including a transoesophageal echocardiogram confirmed the location, anatomy, and pulsatile flow in the two orifices (fig 2B).

Nuclear magnetic resonance imaging showed an aneurysm with a thin epicardial surface and a somewhat muscular isthmus (fig 2C). It also showed a pulsatile pattern of flow into the aneurysm.

At a second radiofrequency ablation procedure one week later, the ablation catheter was advanced into the isthmus of the aneurysm and positioned in the narrowest part of the proximal opening (fig 2D). After a few attempts with scrupulous mapping around the circumference, a successful ablation at 20 W for 30 s was performed with the result that the delta wave disappeared after 2 s. After this attempt only normal anterograde and retrograde conduction over the His bundle was demonstrated. The patient was mobilised a few hours after the procedure and remained haemodynamically stable without any symptoms. The following day an echocardiogram showed no signs of pericardial effusion. At a three month follow up investigation the electrocardiogram was normal and the patient had resumed normal physical activity with no paroxysms of tachycardia.

Discussion

The present case shows that it is possible to perform safe and curative radiofrequency catheter ablation of a posteroseptal accessory pathway located in the isthmus of a coronary sinus aneurysm. Moreover, the present case shows for the first time that it is possible to diagnose the anomaly by echocardiography and nuclear magnetic resonance scanning.

The present case is clinically similar to 10 earlier cases.[1–6] Thus our patient was young and had paroxysmal atrial fibrillation with a very rapid ventricular response and near syncope. During the electrophysiological study the effective refractory period of the accessory pathway was very short. In summary, we report a case of successful catheter ablation of a posteroseptal accessory pathway in which radiofrequency current was delivered in the isthmus of a coronary sinus aneurysm. Patients with posteroseptal accessory pathways who are candidates for ablation with a radiofrequency current catheter should undergo an echocardiographic investigation before the ablation procedure to verify the possible presence of a coronary sinus aneurysm. If an aneurysm is found, coronary sinus contrast angiography should be performed during the ablation procedure to locate the isthmus of the aneurysm, because it is the most likely site for catheter ablation. Finally, we regard it less hazardous to deliver radiofrequency current than low energy DC shocks in coronary sinus aneurysms because they often have thin walls.

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MEASUREMENT

Restenosis after coronary angioplasty: a proposal of new comparative approaches based on quantitative angiography

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Recurrence of coronary artery stenosis or "restenosis" is now well established as the main limitation of percutaneous transluminal coronary angioplasty (PTCA), which was first used by Gruentzig in 1977.[1] However, despite the increasing popularity and application of the percutaneous approach to coronary revascularisation as an attractive alternative to coronary artery bypass graft surgery and the apparent frequency of lesion recurrence there is still no satisfactory universally accepted "definition of restenosis" (table).[2–13] New devices for percutaneous coronary recanalisation (endoluminal coronary stent implantation; directional, extractional, or rotational atherectomy; laser balloon angioplasty; and excimer laser) have up to now, failed to provide better long term outcome than balloon angioplasty.[14–17] but they have stimulated the search for universally applicable, objective methods of assessing the new methods and of comparing them with conventional balloon angioplasty and with each other in terms of the immediate and long term effects on treated vessels.[15]

Nearly all the early reports on restenosis after angioplasty relied on visual or user-dependent analysis of cineangiograms,[2–5 9 10] approaches that are of undoubted clinical value. None the less, the results of these early clinical studies must now be re-examined in the light of information provided by recent technological advances in image acquisition and description, as well as revascularisation hardware.

A selection of different criteria for angiographic restenosis that have been used or are used to describe the outcome of clinical studies

(*a*)	Loss at follow up of at least 50% of the initial gain after PTCA (NHLBI 4).[2]
(*b*)	A return to within 10% of the pre-PTCA diameter stenosis (NHLBI 3).[3]
(*c*)	An immediate post-PTCA diameter stenosis $<50\%$ that increases to $\geqslant 50\%$ at follow up.[3 4]
(*d*)	As for 3 above, but a diameter stenosis $\geqslant 70\%$ at follow up (NHLBI 2).[5]
(*e*)	Loss of $\geqslant 20\%$ diameter stenosis from post PTCA to follow up.[6]
(*f*)	Loss of $\geqslant 30\%$ diameter stenosis from post PTCA to follow up (NHLBI 1).[4]
(*g*)	A diameter stenosis $\geqslant 50\%$ at follow up.[7]
(*h*)	A diameter stenosis $\geqslant 70\%$ at follow up.[8]
(*i*)	Area stenosis $\geqslant 85\%$ at follow up.[9]
(*j*)	Loss $\geqslant$ 1 mm^2 in stenosis area from post-PTCA to follow up.[10]
(*k*)	Loss of $\geqslant$0·72 mm in minimal luminal diameter from post-PTCA to follow up.[11]
(*l*)	Loss of $\geqslant$0·5 mm in minimal luminal diameter from post-PTCA to follow up.[12]
(*m*)	Diameter stenosis $>50\%$ at follow up after successful dilatation of a lesion (defined as diameter stenosis $<50\%$ and a gain of $>10\%$ in luminal diameter immediately after PTCA). Lesions with a $<10\%$ increase in diameter stenosis since PTCA are not included.[13]

(NHLBI 1, 2, 3, and 4 are four different criteria for angiographic restenosis, as defined by the National Heart, Lung, and Blood Institute of the United States.)

The advent of quantitative coronary angiography, which has been pioneered at the Thoraxcenter[18–20] (and is becoming increasingly available with the development of digital cineangiographic equipment for the catheterisation laboratory), has opened up a new approach to clinical restenosis studies. We now describe the evolving concept of "restenosis" through our experience with quantitative coronary angiography over the past ten years,[20–35] and we propose two new approaches to its assessment by absolute luminal diameter measurements obtained by quantitative coronary angiography (*a*) "matching" and (*b*) relative gain, relative loss, and net gain index.

Restenosis: definition difficulties

There are at least 13 different "definitions" of restenosis based on coronary angiography (table). The use of these mainly arbitrary categorical cut-off points, different angiographic follow up rates (57–100%), and visual assessment of the coronary angiogram by most investigators (a method that considerably overestimates lesion severity before PTCA and underestimates luminal narrowing immediately after intervention),[36] largely explains the variability (12–55%) of the reported "incidence of restenosis" (fig 1). Applying three different and frequently used definitions to a series of 490 lesions serially measured during six months follow up, we showed that (*a*) the greatest single determinant of the restenosis rate was the definition applied (fig 2A) and (*b*) even if the eventual incidence of restenosis was similar, different definitions identified different patient populations (fig 2B), making risk factor determination impossible. These factors are almost certainly responsible for most of the confusion surrounding the concept of restenosis after PTCA.

Though some widely used restenosis criteria are based on historical physiological concepts,[37] the measurement used is percentage diameter stenosis, which is calculated by assuming a "normal" diameter value for the segment of coronary vessel immediately proximal or distal to the area of interest and using it as a reference. This assumption has been shown to be invalid, particularly in the context of multivessel

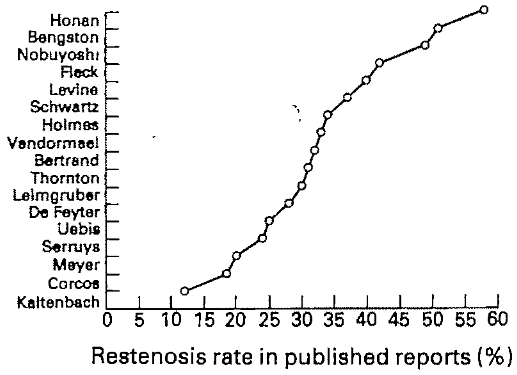

Figure 1 Restenosis rates from a selection of published studies with different angiographic follow up rates (57–100%), follow-up intervals (1–9 months), 11 different restenosis criteria, and various angiographic analysis techniques.

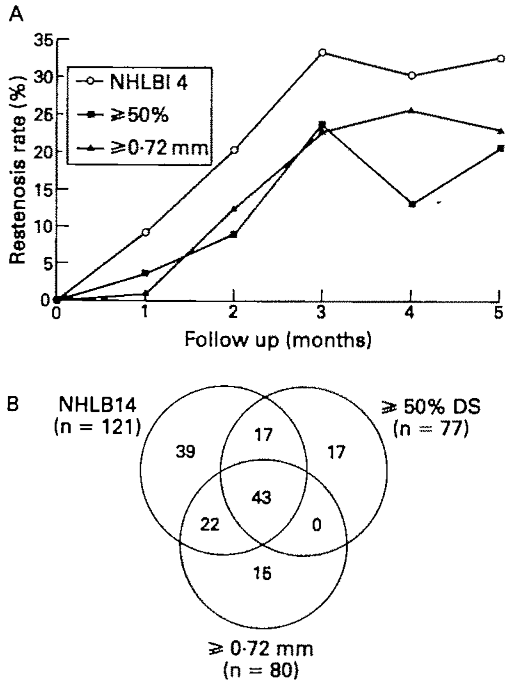

Figure 2 (A) Cumulative incidence of restenosis (defined by three different criteria) during a five month follow up in 490 successfully dilated lesions. NHLBI 4, criterion 4 of the National Heart, Lung and Blood Institute of America (loss of >50% of the initial gain at angioplasty); ≥50%, ≥50% diameter stenosis at follow-up; ≥0·72 mm, 0·72 mm loss in minimal luminal diameter between post angioplasty and follow up (reproduced with permission from Circulation 1988;77:361–71. (B) Venn diagram showing the distribution of lesions fulfilling the different criteria applied in fig 2A. Of a total of 153 lesions showing restenosis according to at least one of the three criteria applied, only 43 fulfil all three. (Reproduced with permission from Circulation 1988;77:361–71[11]).

disease, when there is virtually always diffuse intimal and/or subintimal thickening[38 39] as well as variable age-related or compensatory ectasia,[40] and after interventions when the "reference diameter" may become affected by the restenosis process.[27 41] Approaches that use the percentage diameter stenosis are therefore inherently flawed, both by the computation method and by the inability of a single measurement in time to describe accurately what is essentially a "moving target", as has been shown independently (and almost simultaneously) by our group[11] and by Nobuyoshi *et al*[12] (fig 3). Both groups used predetermined serial angiographic follow up at one, two, three, four and six months to show that luminal renarrowing occurs to some degree in *all* lesions that are dilated and that it is a *continuous*, time-related phenomenon which rarely occurs after six months.

Quantitative angiographic studies have clearly and definitively shown that absolute measurements such as mean luminal diameter, minimal luminal diameter, or the minimal cross sectional area of stenosis provide more reliable and meaningful information than percentage diameter stenosis on the haemodynamic significance of an obstructive coronary lesion.[24–26 29] Of all the measurements directly acquired by quantitative angiography, the absolute value of the minimal luminal diameter has been shown to be the greatest single determinant of the haemodynamic consequences of a stenosis, because this measurement affects blood flow by a fourth power term.[26 42 43] It is therefore the most unambiguous, objective, and reproducible measure to describe the calibre of coronary vessels and changes caused by interventions. All important multicentre trials examining the impact of various pharmacological agents on restenosis after PTCA are now assessed in a core laboratory,[44–46] by quantitatively derived indices—particularly minimal luminal diameter.[47]

Our group has previously recommended the standards required for clinical studies, including sufficient patient numbers, the use of quantitative coronary angiography, 100% angiographic follow up, and restenosis criteria that reflect a significant change in minimal luminal diameter from intervention to follow up.[48] In addition, in a recently published quantitative angiographic study we highlighted the distinction between "clinical" and "angiographic" restenosis,[49] illustrating the dangers of misinterpretation of the results of restenosis studies if observations are based solely on conventional restenosis criteria (for example, >50% diameter stenosis at follow up angiography) without knowledge of the actual changes in luminal dimensions during and after angioplasty. The outcome and conclusions of this study underline the need to define end

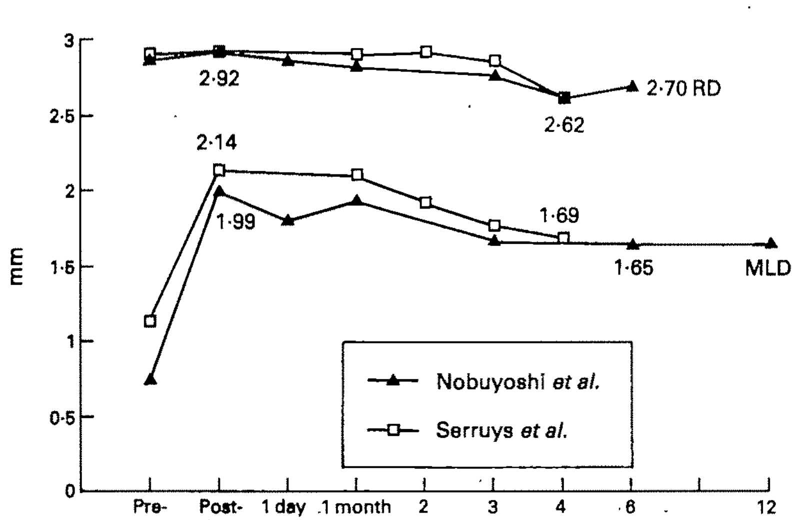

Figure 3 Minimal luminal diameter (MLD) and reference diameter (RD) measurements reported in the studies of Nobuyoshi et al[12] and Serruys et al,[11] showing virtually identical time trends during six month follow up.

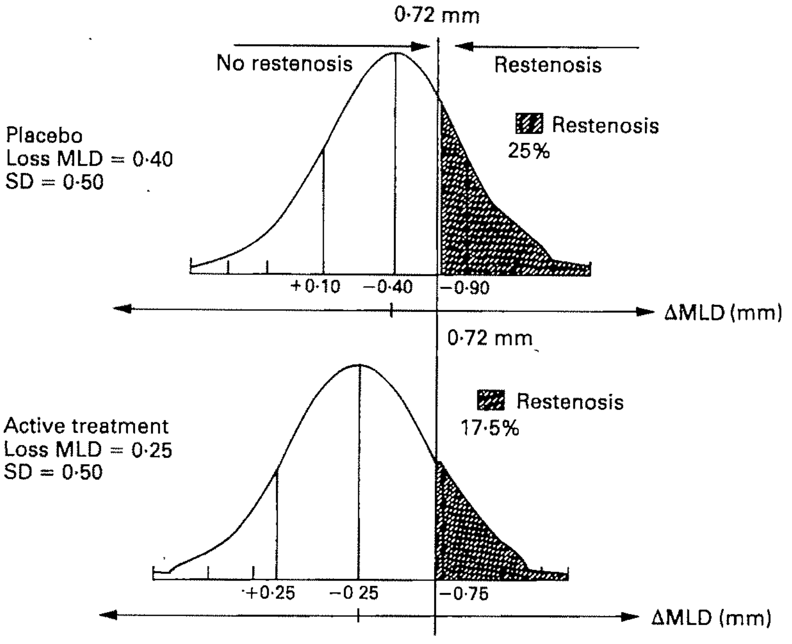

Figure 4 Gaussian model of restenosis in the placebo and treatment groups. The lower curve represents a 30% reduction in the mean deterioration in minimal luminal diameter during follow up (−0·25 mm v −0·40 mm) in the treated group. The upper curve shows the distribution of the change in minimal luminal diameter (Δ MLD) found at follow up in a prospective study at the Thoraxcenter.[11] To show the significance of this difference requires 233 patients per group. Whereas if a deterioration in minimal luminal diameter of 0·72 mm is taken as the cut-off point for restenosis (as shown by the hatched area) 620 patients per group are required. See text for full explanation. (Reproduced with permission of Hogrefe and Huber from Interventional Cardiology.[59])

points for clinical restenosis studies, which we believe must be described as the change in the minimal luminal diameter of the treated lesion immediately after angioplasty (or other intervention) and at follow up.

New criteria for restenosis based on minimal luminal diameter

To develop criteria for restenosis based on the change in minimum luminal diameter seen during follow up, our group measured the long term variability in lesion measurement—ie, 1SD (0·36 mm) of the difference between the means of minimal luminal diameter measurements taken from coronary angiograms of the same lesions 90 days apart when no intervention had been carried out.[23] The actual mean difference in minimal luminal diameter over that period was 0 mm, implying no detectable disease regression or progression that might influence results during the 90 days. The long term variability thus reflects the long term random variation in lesion measurements using the computer assisted analysis system (CAAS). One standard deviation includes 68·3% of the measurement variability and 2SDs account for 95·5%. Therefore a difference in minimal luminal diameter of more than twice the long-term variability can be regarded as indicative of significent change—that is, as a division between restenosis and no restenosis.

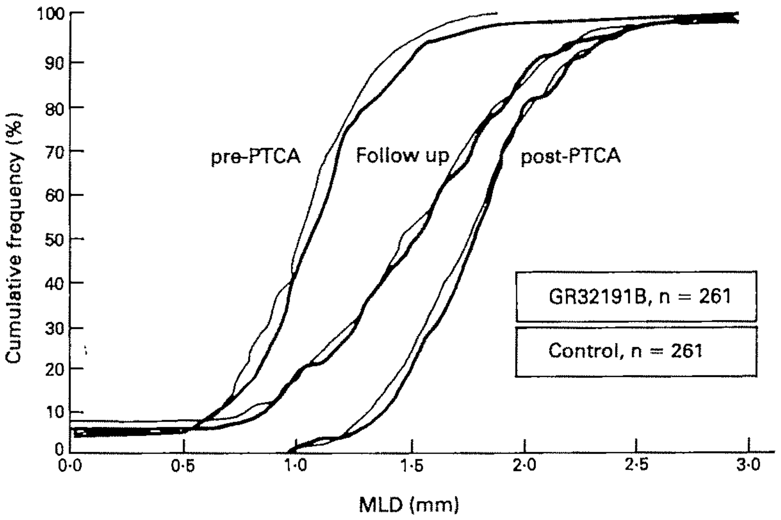

Figure 5 Cumulative frequency (distribution) curves of absolute minimal luminal diameter measurements pre-PTCA, post-PTCA, and at follow up in control (light curves) and treatment groups (heavy curves) for the CARPORT restenosis prevention trial. Virtual superimposition of the curves shows that the groups had similar values for minimal luminal diameter, and that treatment caused no identifiable benefit. (Reproduced with permission from Circulation 1991;84:1568–81.[44])

Ellis and Muller[50] pointed out several limitations to this definition of restenosis that we had previously recognised.[48] Criteria based on absolute changes in minimal luminal diameter did not take blood vessel size into account because the study of variability was performed on vessels with an average reference diameter of 3·7 mm[23] whereas, in two recent large European multicentre restenosis prevention trials the mean diameter of the vessels that were dilated was 2·6 mm.[44 45 51 52] Studies using sliding-scale criteria to overcome this shortcoming have been completed and some initial results have been published.[51 53] We will expand this concept later in this article.

Restenosis: a continuous process

Although reports of pathological studies[54–57] and quantitative angiographic studies[11 12 27] showed that the process of intimal hyperplasia is a continuously distributed phenomenon, the outcome of trials of pharmacological prevention of restenosis and of trials of new interventional devices have been traditionally assessed by categorical cut off criteria for the occurrence of restenosis. When we examined the prospectively collected, carefully standardised, quantitative coronary angiographic data in 1234 patients (1445 lesions) treated by balloon angioplasty, with 91% angiographic follow up, we showed that luminal renarrowing after PTCA, whether assessed by minimal luminal diameter or percentage diameter stenosis, clearly follows a gaussian or normal distribution (fig 4[52]). This finding, like Kuntz *et al*'s[58] findings in patients undergoing atherectomy or stent implantation and previous angiographic evidence provided by our group[11 27] and Nobuyoshi *et al*,[12] provided clinical confirmation of pathological observations and validates the application of parametric statistics to the assessment of restenosis. Furthermore, it shows the limitations of categorical criteria in the assessment of important clinical restenosis trials. There may be sound clinical reasons for selecting particular angiographic definitions of restenosis, but no cut-off point (even one shown to have a physiological basis[37]) can satisfactorily or accurately define a given measure of luminal renarrowing as "restenosis" because this is a continuous process and because there is no identifiable threshold of deterioration in lumen diameter after angioplasty above which physiological or clinical significance is reached.

It is much more realistic and meaningful, therefore, to study the overall effects of a pharmacological agent or revascularisation device in the treated population in terms of its mean effect on the expected loss of minimal luminal diameter for the group (as represented by the mean loss in minimal luminal diameter for the "placebo" or control group). This approach to statistical analysis also has significant implications in terms of the population size required for a valid clinical trial. In the example shown in (fig 5[59]) treatment reduces the mean loss in minimal luminal diameter during follow up after PTCA from 0·40 mm (±0·50 mm) to 0·25 mm (±0·50 mm)—a 30% reduction. If the process is viewed as continuous each treatment group must contain 233 patients if such a difference is to be measured as significant with a power of 90% and a 95% confidence interval. If a categorical approach (restenosis yes/no) is applied to the loss in minimal luminal diameter ($\geqslant$0·72 mm), then the 0·15 mm difference in minimal luminal diameter is equivalent to a reduction in the restenosis rate from 25% to 17·5%. To show that this difference is significant at the 95% confidence level requires 620 patients in each group (266% more patients than needed for the continuous approach).

We believe, furthermore, that the results of intervention trials are more clearly and elegantly presented as simple cumulative distribution curves to show the change in minimal luminal diameter during follow up in treated and control populations (fig 6[44]), or indeed in PTCA and stent or atherectomy groups.[58 60]

New challenges and potential solutions with minimal luminal diameter

The considerable growth in new devices for coronary revascularisation has presented a new challenge in terms of how to describe immediate and long term angiographic outcome. We have tackled the challenge of "comparing the incomparable" by examining their "relative" merits or by confining comparisons to "matched" lesions—that is, lesions of similar severity in vessel segments of identical size and location (even though, contrary to popular belief, luminal renarrowing measured absolutely or as restenosis rates does not vary significantly throughout the coronary tree).[53]

Matching: a surrogate for randomisation

The first method allows us to "compare the comparable" by "matching" the lesions in each treatment group according to three basic principles: (*a*) the angiographic dimensions of the matched lesions are assumed to be identical, (*b*) the observed difference between the two "identical" lesions must be within the range of reproducibility of the computer analysis system being used (for the CAAS system this is ±0·1 mm), and (*c*) the size of the vessels to be matched (interpolated reference diameter) is selected within a range of ±3SD (0·3 mm), giving confidence limits of 99%.[15]

In a recent observational study we compared the immediate angiographic results of balloon angioplasty, directional coronary atherectomy (DCA), and intracoronary stenting by this technique.[15] Both DCA and stenting gave a significantly greater initial improvement in luminal diameter than PTCA. Figure 6A, adapted from a previous observational study,[60] illustrates the application of matching to the comparison of immediate and long-term angiographic outcome after PTCA and DCA. Because the baseline angiographic measurements were similar, the approximate overall gain and loss in minimal luminal diameter can be easily derived from the figure. Though DCA was associated with a significantly greater initial improvement in minimal luminal diameter, the loss during follow up (restenosis) after DCA was also significantly greater than after PTCA, so that the ultimate outcome (minimal luminal diameter at follow up) was similar for both treatments. This technique was used to compare long term results after PTCA and stent implantation in a preliminary study of 93 matched lesions. Though stenting was associated with a greater loss in luminal

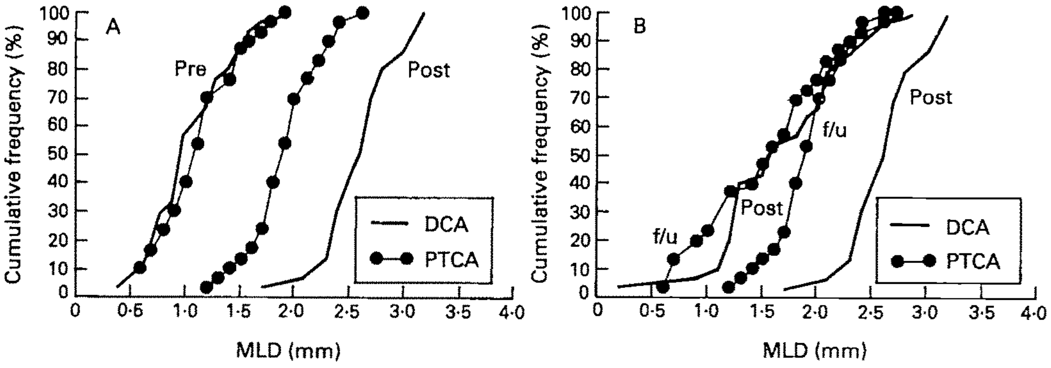

Figure 6 Cumulative frequency (distribution) curves comparing (A) the immediate (pre—post) and (B) the follow up (post—follow up) effects of PTCA and directional coronary atherectomy (DCA) on absolute minimal luminal diameter (MLD) values as measured by quantitative coronary angiography in "matched" coronary lesions. (A) DCA caused a much greater improvement in luminal diameter immediately after intervention. (B) Reduction of this advantage occurred during follow up so that there was little difference between the curves representing minimal luminal diameter at follow up after DCA and PTCA (see text for explanation). (Reproduced with permission from Am J Cardiol 1991;68:1556–63[60]).

diameter during follow up it produced a significantly larger vessel lumen (reflected by a larger MLD) than PTCA at follow up.[61]

Relative gain and relative loss: the sliding-scale and the restenosis paradox

The second method of comparison arose from the need to create sliding-scale criteria to assess the outcome of PTCA in vessels of different sizes; but it may also be used to compare different treatments. As previously explained, the concept of restenosis criteria based on a loss in minimal luminal diameter of ⩾0·72 mm during follow up was developed in vessels with average reference diameter of 3·7 mm[23] so, to overcome this limitation, the concepts of "relative gain" and "relative loss" were introduced to adjust for vessel size, by relating the *absolute* change in minimal luminal diameter after intervention and during follow up to the interpolated reference diameter of the coronary segment in question.[49 51 53] The "net gain index" describes the ultimate outcome of intervention, by relating the net change in minimal luminal diameter from pre-treatment to follow up to the vessel size.

These simple calculations may be presented as follows:

Relative gain = MLD post-intervention − MLD pre intervention/vessel size.

Relative loss = MLD post intervention − MLD at follow up/vessel size.

Net gain index = MLD at follow up − MLD pre intervention/vessel size.

Where MLD is the minimal luminal diameter and the vessel size is represented by the interpolated reference diameter of the lesion pre intervention.

A scattergram of the relative gain and relative loss values for the entire patient population in a recent, large, multicentre, restenosis prevention trial,[45] shows a linear relation (coefficient of correlation 0·4, p < 0·001), with the lines of correlation for placebo and treatment groups being exactly superimposed (fig 7a). This graphic representation confirmed the outcome

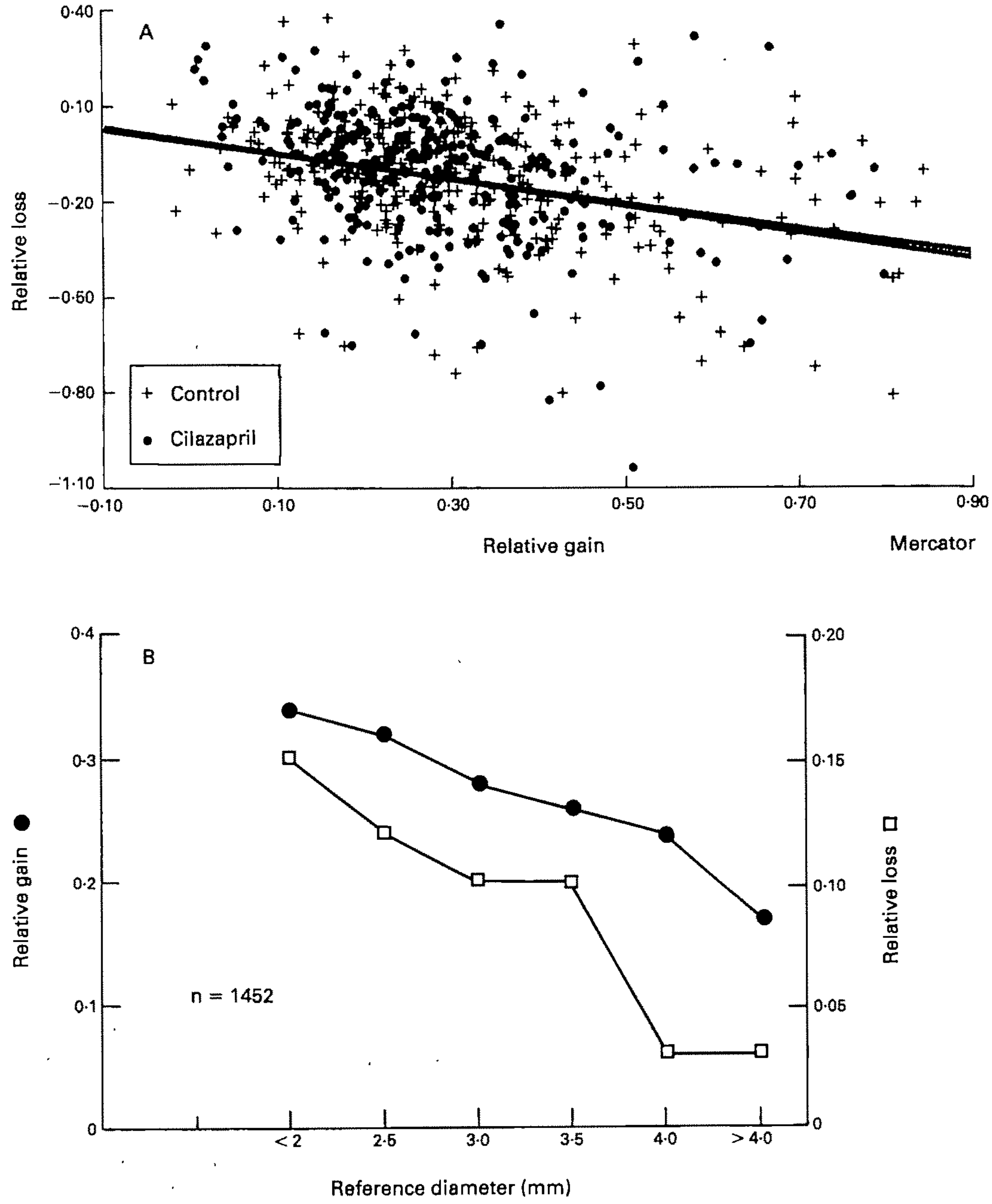

Figure 7 (A) Scattergram of all the values for relative gain at balloon angioplasty and relative loss during follow up in a large multicentre restenosis prevention trial[45] for both placebo and treatment groups. There was an identical linear relation in both groups. (B) Relation between relative gain and relative loss in MLD (from fig 7a) and vessel size (represented by the interpolated reference diameter). The slope of the graph for "relative loss" changed significantly where the vessel size is greater than 3·5 mm in diameter, suggesting less restenosis in larger vessels (see text for explanation).

of the study that had been established with cumulative distribution curves (no demonstrable benefit from the pharmacological agent[45]). More importantly, however, it showed the nature of relation between the relative gain (representing the permanent injury done to the vessel wall by balloon inflation(s)) and the relative loss (the angiographic correlate of intimal hyperplasia or "restenosis"). The regression lines show that the greater the relative gain in minimal luminal diameter achieved by dilatation the greater the subsequent relative loss (that is, a better initial result is subsequently associated with more restenosis). Stepwise multiple linear regression analysis of patient, procedural, and angiographic data from the CARPORT trial[44] also showed that the relative gain is the strongest determinant of restenosis (defined as absolute change in minimal luminal diameter from post-angioplasty to follow up).[51]

This apparent paradoxical association of greater renarrowing of the lumen with greater degrees of luminal improvement by PTCA has recently been reported in a quantitative angiographic clinical study from our group,[49] using absolute measurements of gain and loss in luminal diameter to reflect mechanical wall injury and restenosis respectively. In addition, a pathological study from the Mayo Clinic,[62] of an already well documented porcine model[63] showed (like the clinical study above) a proportional neointimal response to graded vessel wall injury and found that absolute neointimal thickness was more closely related to the coronary artery injury than was percentage diameter stenosis. These studies further support the contention that categorical restenosis definitions are inherently limited in their ability to describe the process of luminal renarrowing after interventions and that quantitative measurements of luminal gain by intervention and loss during follow up are the ideal angiographic correlates of wall injury and intimal hyperplasia.

Ellis and Muller, in an editorial comment on these two studies, recommended the use of absolute measurements, rather than percentage diameter stenosis as a primary angiographic end point for clinical trials.[50] In addition (having pointed out that a change of 0·72 mm has no physiological meaning as a definition of restenosis, unless corrected for the diameter of the reference segment) they recommended normalisation for the diameter of the adjacent vessel at the time of intervention if interventions are carried out in vessels of widely varying calibre. We too[48] had recognised the limitations of using a change in minimal luminal diameter of 0·72 mm as a criterion for significant change in luminal diameter—that is, restenosis—which, it must not be forgotten, was developed in the early years of quantitative angiography.[23] This is why we introduced the concepts of "relative gain", "relative loss", and "net gain index" to describe the immediate and long term angiographic outcome of intervention by any device on a vessel of any size.

In addition to the actual degree of injury to the vessel wall (relative gain in luminal diameter) caused at PTCA, the vessel size itself may have an important influence on "restenosis" (relative loss) which can be characterised by plotting relative gain and relative loss against the vessel size. A threshold of 3·5 mm emerges for the vessel size: vessels with a larger diameter showed a significantly smaller relative loss (p < 0·05[53])—that is, less restenosis, during follow up. Whether this occurrence is a function of decreasing relative gain with increasing vessel size (even though there is no statistically significant difference in relative gain between vessels smaller and larger than 3·5 mm) or is independently related to vessel size itself is not yet clear though logic suggests an interrelation. The application of one of the most frequently used traditional, categorical criteria for restenosis (>50% diameter stenosis) to these data identified no relation between the restenosis rate and either luminal gain at intervention or vessel size[53]: a further illustration of the limitations of this type of approach. Because other groups[7,13,64] used categorical criteria for restenosis and evaluated results according to changes in restenosis rates they did not recognise the association between the proportional luminal improvement after intervention and subsequent deterioration during follow up, despite the use of quantitative angiographic[13] or validated user-dependent[7] techniques and sophisticated statistical analyses.

The relation between relative gain and relative loss achieved with other percutaneous coronary revascularisation devices is being studied but in the light of available evidence from clinical studies from our own institution[14,33,35,60,61] and others,[16,17] and the previously mentioned Mayo Clinic experience in a stented porcine model,[62] there is no reason to expect anything other than a similar or perhaps even stronger proportional relation.

Clinical implications of the paradox

If the "restenosis" phenomenon (angiographically represented by the relative loss) is related to or dependent on the degree of wall injury (relative gain) or the vessel size or both, this information has an important bearing, not only on clinical trails but also for clinical decision making in individual patients. It suggests that the minimal luminal diameter and reference diameter of a "culprit" coronary artery lesion should be accurately measured as an absolute value and be considered with other variables before treatment. As facilities for online digital subtraction quantitative coronary angiography become more widespread it may become possible to reduce the expected long-term relative loss associated with a therapeutic intervention in individual patients by calculation and careful achievement of a moderate relative gain, based on mean values derived from large clinical studies (which should be available in the near future) and by resisting the temptation to aim for a "perfect" angiographic result.

Randomised studies: minimal luminal diameter at follow up as the ultimate end point

Randomised clinical trials are now in progress objectively to compare the long-term benefit of current treatments. Results are eagerly awaited, but how will they be presented? In a randomised population it is assumed that baseline characteristics are similar, in particular the minimal diameter and vessel size of treated lesions. However, the innate differences in the immediate luminal improvements attainable with different treatments and the subsequent deterioration in luminal dimension during follow up suggest that it may not be correct to use the "within patient change in minimal luminal diameter" (that is, the change in minimal luminal diameter from immediately post-intervention to follow up) to compare the various interventions in randomised trials. This argument can be further extended to trials of the pharmacological prevention of restenosis after PTCA. To judge the relative merits of new pharmacological approaches (or new interventional devices) to prevent restenosis in randomised populations the simplest, most objective, and meaningful measurement may be minimal luminal diameter at follow up as the ultimate end point of treatment.

Conclusion

It seems that the greater the relative gain achieved by an intracoronary intervention the greater the subsequent relative loss. This is certainly food for thought for interventional cardiologists, those considering arming themselves with the latest device, and indeed patients (and doctors) with obstructive coronary artery disease contemplating their options.

We suggest that the future of transluminal revascularisation will most likely be shaped and determined by a combined approach of advances in molecular biology or genetic engineering to prevent or control the tissue response to vessel wall injury after intervention rather than simply by altering existing (or introduction of new) therapeutic devices to achieve greater increases in luminal dimensions at intervention. As the search for a solution continues, we propose the matching technique as a temporary surrogate for randomised studies, and the use of relative gain, relative loss, and net gain index as a unifying quantitative angiographic approach to the assessment and comparison of all interventions—pharmacological, mechanical, thermal, or chemical.

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Br Heart J 1992;68:425–9

MEASUREMENT

Effect of increasing heart rate on Doppler indices of left ventricular performance in healthy men

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Abstract

***Objective*—To investigate the effects of heart rate on the Doppler measurements of left ventricular function and to determine the normal pattern of rate dependency.**

***Setting*—University hospital specialising in internal medicine.**

***Participants*—14 healthy male volunteers 10 of whom were studied.**

***Intervention*: Transoesophageal atrial pacing.**

***Main outcome measures*—At paced rates of 70, 80, and 90 ppm the ratio of early to late peak transmitral flow velocity (E/A) was 1·97 (0·28), 1·49 (0·21), and 0·95 (0·11) respectively; the ratio of early to late time-velocity integrals of transmitral flow (Ei/Ai) was 3·03 (0·51), 2·11 (0·24), and 1·14 (0·30) respectively; and the atrial filling fraction (AFF) was 0·17 (0·03), 0·21, (0·04), and 0·24 (0·04) (mean (SD)).**

***Results*—Heart rate showed a linear correlation with E/A (r^2 = 0·806), Ei/Ai (r^2 = 0·838), and AFF (r^2 = 0·343). Neither the peak aortic flow velocity or the mean aortic flow acceleration showed significant changes during pacing at rates of 70, 80, 90, and 100 ppm.**

***Conclusions*—E/A and Ei/Ai can be expected to decrease by 0·5 and 0·9 for each increase of 10 beats/min in heart rate.**

Knowledge of this relation may be useful for the development of algorithms to correct for heart rate when diastolic function is assessed.

(*Br Heart J* 1992;68:425–9)

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Doppler echocardiography is a useful non-invasive procedure for evaluating left ventricular systolic[1,2] and diastolic[3,4] functions. Physiological variables, including the heart rate, affect cardiac performance and Doppler measurements.[5,6] However, the normal pattern of heart rate dependency of those measurements is still unclear. Clarification of the relation between the heart rate and left ventricular performance in healthy individuals would allow the application of echocardiography to be refined. We studied the influence of alterations in heart rate on Doppler indices of left ventricular performance.

Subjects and methods

STUDY POPULATION

We recruited 14 healthy male volunteers; four were excluded because of intolerable discomfort caused by pacing, unsatisfactory Doppler recordings, or a high sinus rate. The remaining 10 men (aged 25–30 (27·2 (1·7)) were free of illness as determined by their history and physical examination as well as by 12 lead electrocardiogram and echocardiogram. We obtained informed consent before the study. The men were fasting, non-sedated, and were receiving no medications at the time of the study.

TRANSOESOPHAGEAL ATRIAL PACING

A 6F quadripolar pacing catheter was passed through the nose and into the oesophagus. The distal or proximal pair of electrodes was used for bipolar pacing and the other pair for monitoring. The initial position was determined as reported by Benson *et al.*[7] Final positioning of the electrode was accomplished by electrocardiographic monitoring during electrode adjustment to obtain consistent left atrial capture. Stable capture required 15 ms pulses of 10 to 22 mA intensity provided by the pacing device (BC02 and BC02EP, Fukuda Denshi, Tokyo, Japan). After electrode placement, the men rested for at least 10 minutes to stabilise heart rate and blood pressure. Echocardiography was subsequently performed at the resting heart rate and was repeated at each paced rate. Atrial pacing was started at a paced rate of 70 ppm. We then increased the rate of atrial pacing by 10 ppm to a maximum of 100 ppm. To ensure haemodynamic stabilisation at each paced rate we waited three minutes before the echocardiogram was recorded. A 12 lead electrocardiogram was also recorded at each paced rate.

ECHOCARDIOGRAPHIC STUDY

Echocardiography was performed with the subject in the supine or left lateral position. A commercial phased array imaging system (SSH 160A, Toshiba, Tokyo, Japan) with pulsed wave and continuous wave Doppler capabilities was used. We used a 2·5 MHz imaging transducer for Doppler echocar-

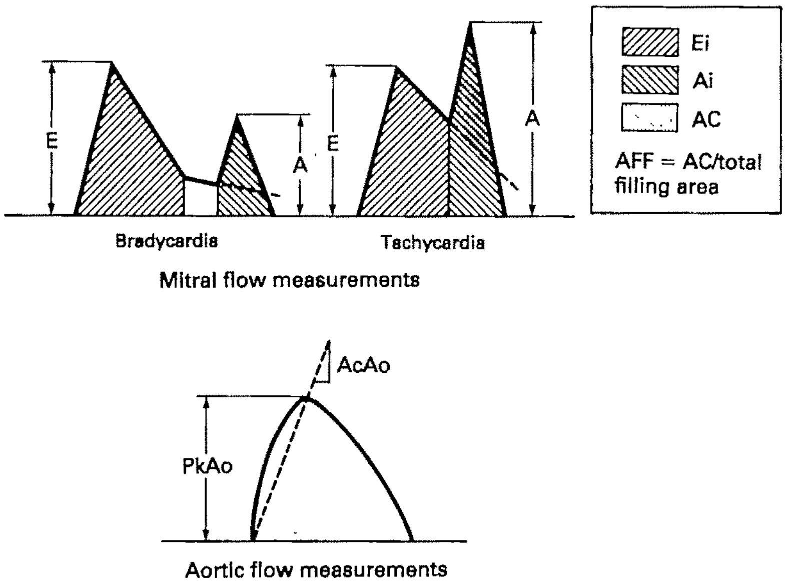


Figure 1 Peak early (E) and late (A) mitral flow velocities and early (Ei) and late (Ai) time-velocity integrals were obtained from the mitral flow velocity curve. The atrial filling fraction (AFF) was determined as the ratio of the area (AC) above the extrapolated line (broken line) from the passive filling wave to the total filling area. Peak aortic flow velocity (PkAo) and mean aortic flow acceleration (AcAo) were obtained from the aortic flow velocity curve.

diography and a 2·5 MHz non-imaging continuous wave Doppler transducer. Doppler recordings of mitral flow velocity were performed with the transducer at the cardiac apex. An apical four chamber view of the heart was used to align the Doppler cursor parallel with the apparent flow direction and the sample volume was placed at the level of the mitral annulus. Then the sample volume was moved slightly (with the aid of the audio signal and spectral display) to maximise the signal-to-noise ratio.

Aortic flow velocities were recorded from the suprasternal notch with a non-imaging transducer angulated to record the maximal flow velocity signal in the ascending aorta.

Doppler signals were recorded on a strip chart at a paper speed of 100 mm/s. The following measurements were obtained from the recordings as shown in fig 1. The mitral flow velocity curve was characterised by the early filling wave (E wave) and late filling wave (A wave). The peak flow velocities of an E wave (E) and an A wave (A) were measured and the E/A ratio was calculated. The time-velocity integrals of an E wave (Ei) and an A wave (Ai) were measured as the area under those flow velocity curves and the Ei/Ai ratio was also calculated. The atrial filling fraction (AFF) was determined by the method of Kuo *et al.*[8] This index was measured as the ratio of the area above the extrapolated line from the passive filling wave (AC) to the total filling area. The peak flow velocity (PkAo) and the mean acceleration from the onset of ejection to PkAo (AcAo) were measured from the aortic flow recording. Each measurement was obtained as a mean value of five consecutive beats to correct for beat to beat variation in the observed values. The mean coefficients of variation of the five observed measurements of the E, A, and PkAo at resting sinus rhythm were 5, 12, and 3%, respectively.

STATISTICAL ANALYSIS

Values are expressed as mean (SD) in the text and as mean (SEM) in the figures. The relation between the measurements and heart rate was analysed by analysis of variance. We obtained the regression line as well as the coefficient of determination (r^2), which was the ratio of the variance associated with the linearity (S_{Lin}) to the total variance of the measurement. The ratio of the S_{Lin} to the variance related to the changes in heart rate (r$'^2$) was also obtained as an index of the

Figure 2 Doppler recording obtained from a representative subject.

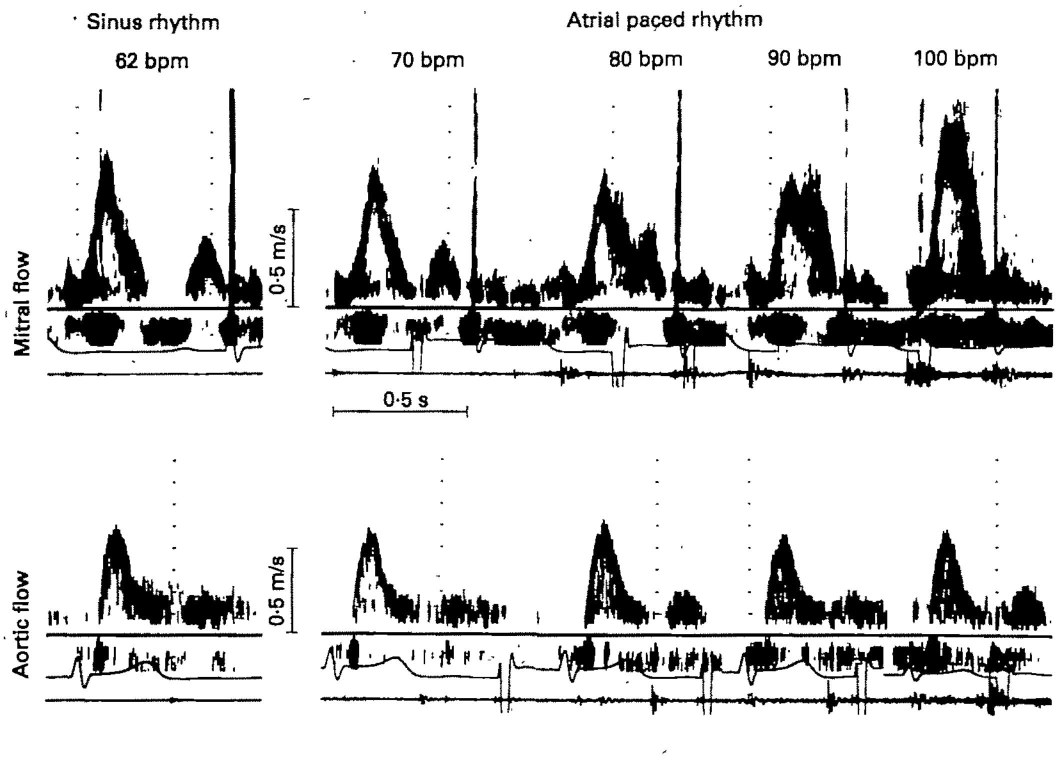
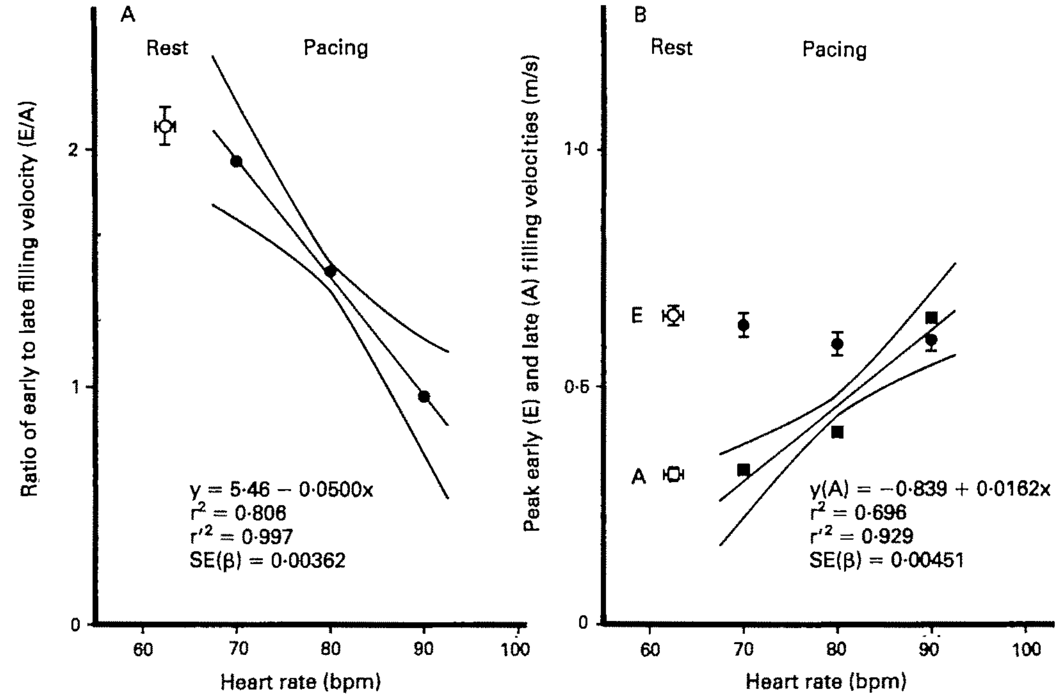


Figure 3 Relation between heart rate and E/A (A), E (circles), and A (squares) (B). The curvilinear lines indicate the 95% confidence interval for the regression lines for a particular point. r^2 = coefficient of determination; r'^2 = coefficient of the linearity of the relation between heart rate and the measurement; SE(β), standard error of the slope of the regression line.



linearity of the relation between the heart rate and the measurement without the influence of other factors, including the intersubject variance and the error. A p value $<0·05$ was regarded as significant.

Results

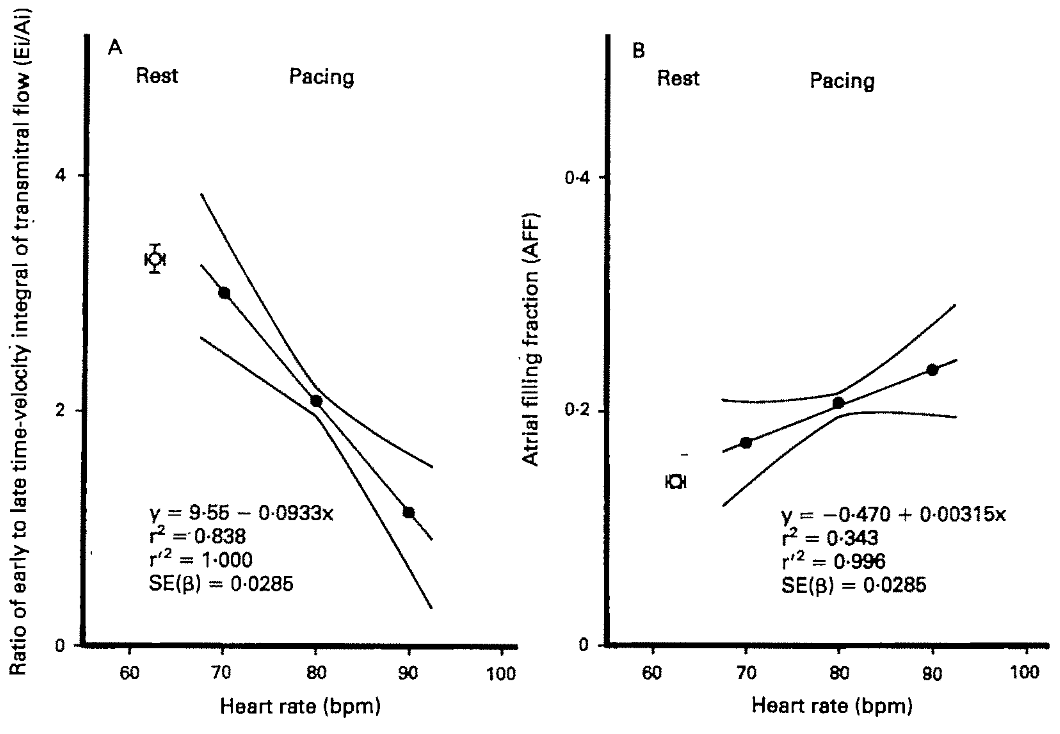
Before pacing the mean heart rate was 62·6 (3·3) bpm. The mean resting systolic and diastolic blood pressures were 125·3 (5·7) and 70·6 (8·3) mm Hg. No abnormalities, including ischaemic ST changes, were seen in the 12 lead electrocardiogram during the study.

Figure 2 shows mitral and aortic Doppler recordings from one man. The transmitral flow pattern apparently changed with increasing heart rate whereas the aortic flow changed only slightly. Data from all the men were analysed as follows.

EFFECT OF ATRIAL PACING ON MITRAL FLOW

An increase in heart rate reduced the E/A ratio (fig 3A). There was an inverse linear relation during pacing (E/A = 5·46 − 0·0500 × HR (bpm) ($r^2 = 0·806$, $r'^2 = 0·997$). Mean values of A during pacing were also significantly affected by a change in heart rate. A was positively correlated with heart rate (A (m/s) = −0·839 + 0·0162 × HR (bpm) ($r^2 = 0·696$, $r'^2 = 0·929$). This relation was somewhat curvilinear. The fact that the variance in the non-linear part of this relation was significant (p

Figure 4 Relation between heart rate and Ei/Ai (A) and AFF (B). See legend to fig 3 for abbreviations.



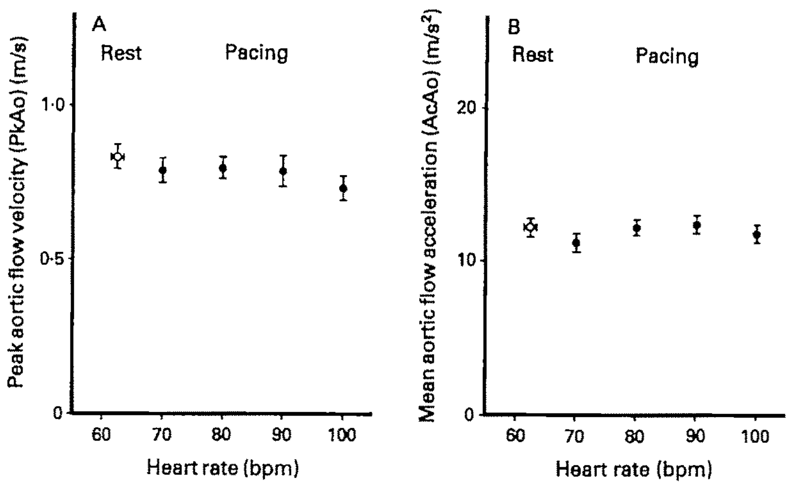


Figure 5 Relation between heart rate and the PkAo (A) and AcAo (B).

$< 0{\cdot}05$) compared with the residual variance supported this observation. E, however, did not change significantly with an increase in heart rate (fig 3B). As with the time-velocity integrals, the Ei/Ai ratio was negatively correlated (Ei/Ai = 9·55 −0·0933 × HR (bpm), $r^2 = 0{\cdot}838$, $r'^2 = 1{\cdot}000$) and AFF was positively correlated (AFF = −0·0470 +0·00315 × HR (bpm), $r^2 = 0{\cdot}343$, $r'^2 = 0{\cdot}996$) with heart rate (fig 4). The AC showed no significant change with pacing rate. An increase in the heart rate to 100 ppm during atrial pacing resulted in overlapping of the A and E waves so that the Doppler indices of mitral flow could not be determined.

EFFECT OF ATRIAL PACING ON AORTIC FLOW

No significant changes in mean values of PkAo and AcAo were seen with increasing heart rate (fig 5).

Discussion

Doppler echocardiography provides blood flow velocity measurements, and various Doppler-derived indices have been used to evaluate cardiac function.[9, 10] However, Doppler echocardiography cannot be simply applied to individuals because those indices can be influenced by various physiological variables. We found linear relations between heart rate and E/A, Ei/Ai, and AFF in 10 healthy young men. This provides a basis for correcting the Doppler-derived indices of left ventricular diastolic function.

MITRAL FLOW VELOCITY MEASUREMENTS

There have been some reports of the effects of heart rate on the diastolic measurements obtained with Doppler echocardiography. Gillam *et al* reported that an increase in heart rate increased the A and decreased E, E/A, and Ei/Ai in the patients with pacemakers.[11] Herzog *et al* showed similar results in patients undergoing cardiac catheterisation.[12] These results suggest that an increase in heart rate may lead to an increase in flow velocity and volume during atrial systole. However, few such studies have been conducted in healthy individuals. Smith *et al* studied the effects of increased heart rate and blood pressure caused by cold immersion in normal volunteers.[13] However, the effect of cold immersion can be attributed to the sympathetic nerve stimulation which may change cardiac function as well as heart rate.[14, 15] Harrison *et al* studied the differences between the E, A, and E/A at a resting heart rate with sinus rhythm and at a heart rate of 90 bpm during transoesophageal atrial pacing.[16] They reported that pacing increased A and reduced E/A. Van Dam *et al* studied the relation between the E/A and resting heart rate and age in healthy volunteers and reported that a higher heart rate was associated with a lower E/A.[17] As the Doppler indices of diastolic function, including the E/A, Ei/Ai and AFF depend on the heart rate, their application to individual subjects requires knowledge of the pattern of their rate dependency. We studied the pattern of the dependency in young healthy men with normal diastolic function.

We found that heart rate correlated closely with E/A and Ei/Ai. Furthermore, because the relation was linear it may be useful in the development of algorithms that will correct for heart rate and enhance the non-invasive assessment of diastolic function in individuals. The pattern of dependency also needs to be studied in individuals with impaired diastolic function.

In addition, the apparent increase in A and in Ai may be attributed to the effect of the superimposition of the A wave onto the descending limb of the E wave. Pearson *et al* reported that PR prolongation increased Ai and that the effect might be caused by superimposition.[18] We too suggested that superimposition might be important in the effect of heart rate on Ei/Ai.[19] The fact that AFF showed only a weak correlation and AC showed no significant correlation with heart rate in the present study supports this concept.

Our present study had some limitations. There was a small but significant increase in the interval between the pacing artefact and the QRS complex (187 (14), 207 (15), and 217 (19) ms at paced rates of 70, 80, and 90 ppm, respectively). Because an increase in PR interval (as well as an increase in heart rate) causes more superimposition, the effects of changes in heart rate may have been enhanced in the present study.

AORTIC FLOW VELOCITY MEASUREMENTS

Aortic flow velocity and acceleration are known to reflect the left ventricular systolic function.[1, 2] Some investigators have studied the effects of heart rate on aortic flow measurements. Wallmeyer *et al* reported that the peak aortic flow velocity as well as the mean acceleration of aortic flow showed a strong correlation with the max dP/dt and max dQ/dt and was independent of the heart rate in dogs.[20] On the other hand, Harrison *et al* in a study of healthy volunteers found an inverse relation between the heart rate and peak aortic flow velocity and acceleration.[5] They attributed this to a decrease in the end diastolic volume caused by the increased heart rate. We found no relation between aortic flow measurements and heart rate. Harrison *et al* compared the aortic flow measurements at the resting heart rate and at heart rates of from 90 to 150 ppm during atrial pacing, whereas we used paced rates of from 70 to 100 ppm. At these low rates a change of heart rate may produce only minimal changes in the Doppler-derived systolic measurements. The relation between heart rate and measurements of aortic flow and mitral flow in health and disease should be further investigated.

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Br Heart J 1992;**68**:430–3

AUDIT

Cardiac surgery: moving away from intensive care

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Abstract

***Objective*—To evaluate outcome in patients managed outside an intensive care unit after open heart surgery.**

***Background*—The high cost of cardiac surgery is mainly due to the needs of traditional postoperative care. The requirements for intensive care and treatment has decreased with improvements in techniques of cardiac surgery and anaesthesia. In this setting the need to continue to depend on intensive care units for the recovery of cardiac surgical patients is questionable on clinical and economic grounds.**

***Design*—Postoperative outcome in 245 patients over a four month period was studied prospectively.**

***Patients*—Mean age of the patients was 63·2 years. They underwent a wide variety of operative procedures. Ninety percent of them recovered in a dedicated three bed cardiac surgical recovery area where the management protocol led to rapid extubation and step down in dependency care.**

***Results*—Median time for ventilatory support was 90 minutes after transfer to the area. Only five patients were subsequently admitted to the general intensive care unit for prolonged respiratory and cardiac support. Ten patients were electively admitted to the general intensive care unit. Two deaths occurred in hospital in this group (0·8%). Four patients were ventilated for 24 hours in the recovery area itself and made an uncomplicated recovery.**

***Conclusion*—This study confirms that over 90% of patients undergoing cardiac surgery would recover safely and be treated effectively in a more economical aréa than intensive care.**

(*Br Heart J* 1992;68:430–3)

The past decade has seen a substantial increase in the demand for cardiac surgery principally through the acknowledged benefits of myocardial revascularisation. Cardiac surgery proves cost effective in terms of quality adjusted life years by improving capacity for work, longevity, and quality of life in all age groups[1] This is, however, an expensive speciality and if we can reduce the cost of heart operations, the procedures may achieve still higher priority. The single factor that differentiates open heart surgery from other forms of surgery is cardiopulmonary bypass (CPB). Cardiac surgical patients traditionally occupy high dependency beds in an intensive care unit for up to 36 hours because of the damaging effects of cardiopulmonary bypass and prolonged anaesthesia.[2,3] In Oxford an intensive care bed costs over £750 and a recovery bed around £380 a day. Does modern cardiac surgery justify this expense or can costs be reduced without compromising safety by a fresh approach to the practical and organisational aspects of the speciality?

Improvements in extracorporeal technology with membrane oxygenation, arterial line filtration, and blood sparing techniques have reduced the cerebral, pulmonary, renal, and bleeding complications of cardiopulmonary bypass. Most cardiac operations are immediately beneficial when patients have surgery at an early stage of their disease.[4] Changes in anaesthetic and perfusion techniques now routinely allow extubation within two hours of surgery in a cardiac recovery area within the operating theatre complex. This produces a rapid step down in dependency level and therefore lower costs. The results of postoperative care for 245 consecutive adult patients undergoing both elective and emergency open heart surgery at the Oxford Heart Centre have been analysed.

Patients and methods

Between 1 January and 30 April 1990, 197 men

Table 1 Cardiac surgery in Oxford Heart Centre January to April 1990 (a four month period, n = 245)

Type of operation	*CABG*	*MVR*	*AVR*	*AVR and MVR*	*CABG and valve(s)*	*Miscellaneous*
No	167	17	28	4	19	10
Age (mean (range)) (y)	60 (38–76)	62·3 (35–76)	62 (37–75)	56·5 (49–62)	69·3 (63–75)	37·6 (20–64)
Hospital stay (mean (SD)) (days)	7·3 (2·2)	8·5 (2·0)	8·2 (2·4)	7·8 (1·7)	8·3 (2·0)	6 (1·0)

Hospital deaths, two (0·8%); CABG, coronary artery bypass grafts; MVR, mitral valve replacement; AVR, aortic valve replacement.

and 48 women underwent cardiac surgery with cardiopulmonary bypass. The mean age for all the patients was 63·2 (range 20 to 77) years (table 1). Ninety seven (39·5%) patients were older than 65. Two separate areas were designated for adult postoperative care. Firstly, and preferentially, a three bed cardiac surgical recovery area within the operating theatre complex, and secondly the general intensive care unit, which had previously been used routinely to admit all patients after open heart surgery.

The cardiac surgical recovery area has facilities for intermittent positive pressure ventilation, continuous monitoring of the electrocardiogram, arterial and central venous pressure, and provisions for basic cardiovascular support. This unit operates continuously from Monday to Saturday morning, but unlike the general intensive care unit, it is not routinely staffed at the weekend.

Transfer of patients to the general intensive care unit was based on specific criteria. These included preoperative multisystem organ failure, very poor left ventricular function requiring prolonged intra-aortic balloon pump support, poor respiratory function with special ventilatory requirements, and patients who sustained an unexpected event preoperatively. It was estimated that this would amount to 5%–7% of the adult practice. All other patients including those after cardiac reoperation, acute aortic dissection, double valve replacement, or patients with preoperative renal failure requiring haemodialysis were managed in the cardiac surgical area.

Patients operated on and extubated in the morning were transferred to the cardiac surgical floor in the afternoon allowing one recovery bed to be used twice. Because five to six adult open heart operations were performed each day, restriction of the cardiac surgical recovery area to three beds meant that, for logistical reasons a small proportion of patients who would normally be admitted to this area were cared for in available general intensive care beds.

SURGICAL TECHNIQUES

All surgical procedures were performed with cardiopulmonary bypass using a Cobe CML membrane oxygenator and Pall 40 μm arterial line filter. Table 1 summarises the operations performed. Coronary artery bypass surgery was undertaken with either cold potassium cardioplegia and moderate hypothermia (30 −32°C) (n = 89) or intermittent aortic cross clamping and fibrillation (n = 78). All valve replacements were performed with cold potassium cardioplegia and moderate systemic hypothermia, as were combined valve plus coronary bypass procedures and other operations. Patients were rewarmed to 37°C before weaning from cardiopulmonary bypass.

ANAESTHETIC TECHNIQUES

All drugs apart from aspirin were continued until the morning of operation. Patients were premedicated with 10–20 mg papaveretum and 0·04 mg hyoscine intramuscularly. Before the induction of anaesthesia radial arterial and peripheral venous access was made under local anaesthesia. With an electrocardiogram and monitoring arterial pressure anaesthesia was induced and maintained with fentanyl (10–15 μg/kg) and thiopentone (1–3 mg/kg) or etomidate (0·1–0·3 mg/kg), and pancuronium bromide (0·15 mg/kg). After endotracheal intubation a triple lumen central venous cannula was inserted into the right internal jugular vein. Anaesthesia was maintained with nitrous oxide and halothane. Glyceryl trinitrate infusion was used to control hypertension.

During cardiopulmonary bypass the patient received a continuous infusion of propofol (4–6 mg/kg/h) and atracurium (0·5 mg/kg). At the end of the procedure patients were given 0·5 mg glycopyrrolate with 2·5 mg neostigmine to reverse the residual muscle paralysis, and were transferred to the cardiac recovery area or intensive care unit.

POSTOPERATIVE MANAGEMENT

After admission to the cardiac surgical recovery area all patients were weaned from ventilatory support as soon as they established haemodynamic stability and stopped bleeding. When the patients regained consciousness intermittent positive pressure ventilation was discontinued and they were connected to a Mapleson C circuit with an oxygen flow of 6 l/min and allowed to breathe spontaneously.[5] The patient remained intubated until satisfactory gas exchange was achieved as confirmed by serial arterial blood gas analysis. These are judged as being within acceptable parameters if on an inspired oxygen fraction of $<0·5$ the Pao_2 is >10 kPa and $Paco_2$ is $\leqslant 7·5$ kPa. Unless extubated in the operating theatre itself, the decision to wean and extubate patients was initiated by the specially trained nursing staff of the cardiac surgical recovery area. Throughout the weaning process and after extubation arterial blood gas analysis and pulse oximetry were closely monitored. Postoperative analgesia was achieved with a morphine infusion at 1–3 mg/h. An early postoperative chest *x* ray film was only obtained if clinically indicated. Usually the first chest *x* ray film was taken after removal of the chest drains.

The time of discharge from the cardiac surgical recovery area depended on the number of operations planned each day. The fittest patients were operated on early in the day to facilitate uncomplicated recovery and transfer to the floor within four to six hours of operation, allowing reuse of the recovery space.

Results

We studied 245 consecutive patients of which 48 (19·6%) were women.

ADMISSION TO CARDIAC SURGICAL RECOVERY AREA

Two hundred and twenty (90%) patients were electively admitted to the cardiac surgical recovery area, 70% after coronary artery bypass surgery, the rest mostly after simple or combined valve operations. The miscellaneous group of 10 patients included two patients who had composite aortic root replacement with

Table 2 Site of postoperative recovery

	Adnussions to recovery area	*Admission to general internal care unit*
CABG	153 (91·6%)	14
AVR	27 (96·4%)	1
MVR	14 (82·3%)	3
AVR and MVR	4 (100%)	0
CABG and valve(s)	13 (68·4%)	6
Miscellaneous	9 (90%)	1
Total	220	25

Footnotes as for table 1.

Table 4 Median duration of ventilatory support in cardiac surgical recovery area

	Duration of ventilatory support	*Extubation time (min)*
CABG	60	120
AVR	120	150
MVR	90	135
AVR and MVR	210	240
CABG and valves	65	125
Miscellaneous	10	30

Footnotes as for table 1.

reimplantation of the coronary arteries. Of the 167 patients undergoing coronary artery bypass surgery (mean (SD) grafts/patient were 2·8 (0·6)) at least one internal mammary artery was used in 55% of cases. Ninety eight patients (58·7%) had three grafts or more. Fifty eight patients (85·3% of all valves) were admitted to the cardiac surgical recovery area after valve replacement; of these 17 (29%) had combined coronary artery bypass graft and valve surgery or underwent double valve replacement (table 2).

Total time (mean (SD)) on cardiopulmonary bypass ranged from 45 (13·9) minutes for mitral valve replacement to 79 (22·2) minutes for double valve replacement (table 3). Patients undergoing coronary artery bypass surgery (68·2%) were on cardiopulmonary bypass for 57 (15·7) minutes with a mean aortic cross clamp time of 32 (11·9) minutes.

EXTUBATION TIME

The median time on ventilatory support after admission to the cardiac surgical recovery area was 90 minutes (range 0–18 hours) with removal of the endotracheal tube (table 4) at a median time of 120 minutes (range 0–18 hours). The mean Pao_2 and $Paco_2$ (table 5) were 14·38 (4·26) kPa and 6·23 (0·63) kPa at two hours and 16·68 (4·0) kPa and 6·02 (0·64) kPa at four hours after extubation respectively. The inspired oxygen fraction was 0·25–0·3 on a variable flow oxygen mask with a four litre oxygen flow. Four patients (1·8%) required reintubation after early extubation (one for respiratory apnoea) and three patients were returned to the operating theatre for excessive bleeding. Four patients (1·8%) were assessed to be unfit for safe return to the general floor on the next day and continued to be managed in the cardiac surgical recovery area for more than 24 hours.

MORTALITY

There were two deaths (0·8%). One 46 year old woman with triple vessel disease and recent myocardial infarction died after coronary artery surgery. She had had bilateral varicose veins stripped, and she received two saphenous vein homografts one of which was acutely rejected and thrombosed soon after operation. She died from an extension of her myocardial infarction 11 hours after operation. The second patient was a 64 year old man with severe mitral valve disease who died following acute dissection of the ascending aorta three days after the initial operation.

Table 3 Mean (SD) duration of operation, cardiopulmonary bypass, and aortic cross clamp times (min)

	Duration of operation	*Duration of bypass*	*Duration of cross clamp*
CABG	152 (36)	57 (15)	32 (12)
AVR	144 (35)	57 (18)	45 (12)
MVR	133 (19)	45 (14)	31 (11)
AVR and MVR	171 (23)	79 (19)	64 (18)
CABG and valves	187 (34)	75 (17)	56 (14)
Miscellaneous	113 (28)	20 (5·5)	11 (3)

Footnotes as for table 1.

ADMISSION TO THE INTENSIVE CARE UNIT

Twenty five patients were admitted to the intensive care unit. Of these, 10 (40%) patients were admitted due to lack of space in the recovery area. Five patients (2·25%), having been initially admitted to the cardiac surgical recovery area, were transferred to the intensive care unit for prolonged inotropic and respiratory support on the operative day (table 6). Ten patients were electively admitted to this area on the basis of their preoperative assessment.

HOSPITAL STAY

The mean duration of postoperative hospital stay (table 1) was 7·5 (95% range 5–12) days. Sixty eight per cent of coronary artery bypass patients were discharged on the sixth postoperative day. The Oxford Heart Centre allocates 3·7 nursing staff for each recovery bed as opposed to 7·2 for a bed in the general intensive care unit. The cardiac recovery area is staffed only during weekdays, unlike the general intensive care unit, which is staffed at a constant level for seven days a week irrespective of patient workload. Particularly cost effective in the cardiac surgical recovery area is the rapid turnover with a single recovery bed used for more than one patient in 24 hours.

PRESENTATION OF DATA

All data are presented as means (SD) where the results are normally distributed and as medians were the distribution is not normal.

Discussion

Advances in anaesthetic, surgical, and perfusion techniques have resulted in an improved outcome after cardiac surgery. Attitudes towards postoperative care, however, have not kept pace with these improvements. Our hypothesis was that attenuation of the damaging effects of cardiopulmonary bypass, in

Table 5 Arterial blood gases (mean (SD) partial pressure) after extubation in the postoperative period

	Before extubation	2 h after extubation	4 h after extubation
Pa_{O_2} (kPa)	21·86 (7·7)	14·38 (4·26)	16·68 (4·0)
Pa_{CO_2} (kPa)	4·93 (0·9)	6·23 (0·63)	6·02 (0·64)
pH	7·38 (0·06)	7·29 (0·04)	7·31 (0·03)
Base excess	−2·7 (1·7)	−3·9 (2·5)	−2·6 (2·13)

association with a shorter operative and anaesthetic time, would allow safe and early extubation with a rapid step down in medical and nursing dependency care. In this prospective study of common adult cardiac surgical procedures we have shown that postoperative recovery can be safely managed outside a conventional intensive care unit in 90% of patients.

Age is not an adverse factor in selecting patients for this type of postoperative care. Almost 40% of the patients recovered in this facility were over 65 years old. The range of the surgical procedures confirmed the preponderance of surgery for ischaemic heart disease, and showed that patients with long standing valvar disease may be safely managed in this way. In fact, 85·8% of patients undergoing isolated or combined valve procedures were managed in the cardiac surgical recovery area.

Contemporary techniques of open heart surgery have led to an appreciable reduction in aortic cross clamp, cardiopulmonary bypass, and total operating time. In this series 84·5% of the operations were completed within 90 minutes from incision to closure (table 3). Expeditious surgery prevents early complications that are associated with inadequate myocardial preservation or excessive bleeding. Bleeding is particularly related to extended cardiopulmonary bypass. It is also generally accepted that prolonged exposure of the open wound is more likely to produce infective complications and thereby delay discharge of the patient from hospital.

Modification of the anaesthetic protocol[6] to complement the advances in surgery has in turn allowed the rapid weaning of patients from ventilatory support and early extubation. The decision to extubate depends generally on the overall clinical picture and more specifically includes assessment of the conscious level of the patient and the ability to respond to commands, ability to breathe spontaneously and comfortably at a respiratory rate not exceeding 30 breaths a minute, and haemodynamic stability with acceptable blood loss.

Table 6 Reasons for admissions to intensive care unit after cardiac surgery

	No
Preoperative clinical decision	15
Lack of space in cardiac surgical recovery area	10
*Transfers from cardiac surgical recovery area after elective admission	5

*These patients were admitted to the intensive care unit after elective admission to the cardiac surgical recovery area, where their clinical status required them to have a prolonged ventilatory or cardiovascular support.

Measurement of blood gases allows supportive evidence of uncomplicated recovery. In only nine patients (4%) did this policy prove inappropriate. It is possible that more detailed preoperative assessment of this group of patients would have led to their elective admission to the general intensive care unit.

Early extubation and rapid step down in dependency has both clinical and economic benefits. Early mobilisation, and return to normal nutrition have led to a shorter stay in hospital. Conventional intensive care had included elective postoperative ventilation for unnecessarily long periods. This, compounded by unnecessary sedation, led to delays in returning the patient to a normal ward and a protracted recovery. Reductions in the period of intubation, sedation, ventilation, and thus recovery time led to a rapid reduction in nursing dependency and hence nursing workload and supportive treatment. Most patients (68·1%) are discharged on the sixth postoperative day.

The final arbiter of this modified management of cardiac surgery patients must be patient morbidity and mortality. In this series a mortality of 0·8% for 245 consecutive patients with a wide range and severity of cardiovascular problems supports the abandonment of the general intensive care unit for a more economical alternative; only a small group of patients "failed" this concept of postoperative cardiac care.

The recommended ratio of nurses to a bed in an intensive care unit is 7·2. The requirement in the cardiac recovery area is 3·7. The cost of an intensive care bed in this unit is £750 per day, whereas the recovery facility costs £380 a day. Also, short operating times allow for early extubation, so a particular bed is used twice in 24 hours.

These results support our initial contention that less than 7% of open heart patients require intensive care after surgery. The size and extent of an operation do not determine the need for intensive care, only conditions shown in a complicated medical history to require prolonged intensive care serve as criteria for admission to intensive care. Our experience has shown that admission of routine cardiac surgical patients to a general intensive unit is both unnecessary and a waste of resources.

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Br Heart J 1992;68:434–6

AUDIT: BRITISH CARDIOVASCULAR INTERVENTION SOCIETY REPORT

Cardiac interventional procedure in the United Kingdom during 1990

Peter J B Hubner on behalf of the British Cardiovascular Intervention Society

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The British Cardiovascular Intervention Society asked cardiac units that performed adult and paediatric interventional procedures for information on the procedures that had been performed between 1 January and 31 December 1990. This was the third year of this form of audit. Records were obtained from 51 adult cardiology units including nine private hospitals. There were two fewer units than in the 1989 survey because two units had combined (National Heart Hospital and Brompton Hospital) and one unit, the Victoria Infirmary Glasgow, was unable to provide any information on its interventional procedures. There were 21 paediatric cardiology units, defined in this report as any hospital performing paediatric cardiological interventional procedures. In this report there were five new units which were not included in the 1989 report. One private unit from the 1989 survey did not perform paediatric procedures in 1990 (see appendix A). The results of this survey should be read in conjunction with those of 1988 and 1989.[1 2]

Table 1 Percutaneous transluminal coronary angioplasty in 1990

Country	*No/million population*
United States	1072
Belgium	569
Holland	545
West Germany	543
Canada	453
France	400
Switzerland	354
Austria	229
Japan	200
United Kingdom	148
Italy	79
Spain	60

Source: Intervention Ltd, 1 Redman Court, Bell Street, Princes Risborough, Buckinghamshire.

Table 2 Percutaneous transluminal coronary angioplasty in the United Kingdom in 1990: Number of procedures per annum in 51 cardiac units

Procedures	*Units*
0–50	5
51–100	11
101–150	11
151–200	5
201–250	5
251–300	7
301–350	6
351–400	0
401–450	1

Percutaneous transluminal coronary angioplasty

NUMBER OF PROCEDURES

There were 8459 procedures recorded (148 per million population). The rate of increase from 1989 was 18% compared with a 42% increase from 1988 to 1989. Table 1 compares the United Kingdom figures with those of other countries. In 1990 13·2% of total percutaneous transluminal coronary angioplasty procedures were performed in private hospitals. The number of cardiac units performing 150 or more procedures a year increased from 23 to 24 (table 2).

Table 3 Percutaneous transluminal coronary angioplasty in the United Kingdom during 1990: data from 51 cardiac units and 8459 procedures

Data	*Mean (%)*	*Range (%)*
Mortality (7840)	0·71	0–3·2
Emergency coronary artery bypass grafting (7818)	2·14	0–11·1
Myocardial infarction (6698)	1·91	0–8·5
Success (7229)	86	59–100

Numbers in parentheses are the total number of procedures for which information was available.

RESULTS OF PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Some units were unable to provide full data in response to all the questions that were asked. The results in this survey and its tables show the number of cardiac units and the number of procedures from which the information was derived.

The overall results of coronary angioplasty and the results from single vessel dilatation and from multivessel dilatation in 1990 are shown in tables 3–5. The overall results for 1990 were similar to those of 1989. Mortality for single vessel dilatation progressively increased from 0·37% in 1988, to 0·42% in 1989, and to 0·62% in 1990. The emergency coronary artery bypass graft rate during these years was 2·3, 1·6, and 2·0% respectively. Eighty three percent of percutaneous transluminal coronary angioplasty procedures were for single vessel dilatation—that is, for true single vessel disease or where one vessel was dilated in the presence of multivessel disease. For multivessel dilatation the average number of vessels dilated was 2·1. The mortality between 1988 and 1990 fell progressively from 1·6% in 1988, to 1·3% in 1989, and to 1·1% in 1990. The emergency

Table 4 Percutaneous transluminal coronary angioplasty in the United Kingdom in 1990: single vessel dilatation (data from 45 cardiac units)

Data	*Mean (%)*	*Range (%)*
% of total percutaneous transluminal coronary angioplasty (6012)	83	54–100
Mortality (5673)	0·62	0–2·9
Emergency coronary artery bypass grafting (5673)	2·0	0–11
Myocardial infarction (5189)	1·6	0–4·2
Success (5460)	86	68–100

Numbers in parentheses are the total number of procedures for which information was available.

Table 5 Percutaneous transluminal coronary angioplasty in the United Kingdom in 1990: multivessel dilatation (data from 43 cardiac units)

Data	*Mean (%)*	*Range (%)*
% of total percutaneous transluminal coronary angioplasty (1462)	18	0–46
Mortality (1376)	1·1	0–20
Emergency coronary artery bypass grafting (1258)	2·6	0–18
Myocardial infarction (1004)	2·9	0–18
Success (1179)	87	40–100

Numbers in parentheses are the total number of procedures for which information was available.

Table 6 Percutaneous transluminal coronary angioplasty in the United Kingdom in 1990: clinical indications

	Unstable angina	*Post thrombolysis*	*Acute myocardial infarction*	*Repeat Percutaneous transluminal coronary angioplasty*	*Chronic occlusion*	*Previous Coronary artery bypass grafting*
Cardiac units	34	26	26	42	39	38
Total procedures	1349	356	146	902	808	514
Mortality (%)	0·8	2·2	5·9	0	0·4	1 1
Emergency coronary artery bypass grafting (%)	3·3	1·7	5·3	1·8	1·4	1·1
Myocardial infarction (%)	3·0	2·8	3 8	0·8	0 4	1·7
Success (%)	86	88	79	91	58	86

coronary artery bypass rate rose from 1·7% to 2·6% between 1989 and 1990.

CLINICAL INDICATIONS FOR PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (TABLES 6 AND 7)

The results were similar to those of 1989. The definitions of unstable angina, post-thrombolysis, and acute myocardial infarction are the same as those used in the 1989 report.

OTHER CORONARY INTERVENTIONAL PROCEDURES (TABLE 7)

A small number of non-coronary angioplasty procedures were performed. Only information on the number of procedures was requested as this was the first year that these procedures had been surveyed.

RELATION BETWEEN CARDIAC CATHETERISATIONS AND PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTIES (TABLE 8)

When all cardiac catheterisations for coronary artery and valvar heart disease in adults were included 13% (range 2–32%) of procedures later led to percutaneous transluminal coronary angioplasty.

SURGICAL COVER FOR PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

As in the 1989 survey interest and debate over surgical cover[3,4] prompted a separate analysis of the results of the six cardiac units without on site cardiac surgical facilities (table 9). The requirement for emergency coronary artery bypass graft surgery was lower in the centres without on site surgery. This, however, was not at the expense of significant increases in mortality or myocardial infarction.

Table 7 Percutaneous transluminal coronary angioplasty in the United Kingdom in 1990: other procedures

Procedure	*Centres*	*Numbers*
Rotacs	6	35
Stents	2	13
Atherectomy	5	15
Laser balloon	1	7
Excimer laser	1	65

Table 8 Relation between catheterisations and percutaneous transluminal coronary angioplasties (data from 46 cardiac units)

	Range
Total catheterisations (58197)	274–3300
Total percutaneous transluminal coronary angioplasties (7445)	10–428
Going from percutaneous transluminal coronary angioplasty to catheterisation (13%)	2–32%

Balloon dilatation of valves in adults (table 10)

The frequency of balloon dilatation of aortic valves continued to fall whereas that for balloon dilatation of the mitral valve nearly doubled, from 112 in 1989 to 213 in 1990.

Paediatric interventional procedures (table 11)

The total number of procedures increased by 26% since 1989. The range of procedures widened to include dilatation of subaortic stenosis and closure of ventricular septal defects. The paediatric interventional procedures had a low mortality and morbidity with the exception of balloon dilatation of the aortic valve.

Comments on the 1990 survey of procedures

Many cardiac units still had difficulty in providing complete data; there was no improvement since the 1989 audit.

The number of percutaneous transluminal coronary angioplasties per million population in the United Kingdom during 1990 remains considerably lower than that of the United States and many other countries of Western Europe. The mortality for single vessel dilatation has increased each year from 1988 to 1990. The requirement for emergency

Table 9 Percutaneous transluminal coronary angioplasty in the United Kingdom in 1990: comparison between cardiac units with on site and off site surgical facilities

	On site	*Off site*
Cardiac units	45	6
Numbers	7878	581
Mortality	56/7259 (0·77%)	0/581
Emergency coronary artery bypass grafting	161/7259 (2·2%)	6/559 (1·1%)
Myocardial infarction	115/6139 (1·9%)	13/559 (2·3%)

Table 10 Balloon dilatation of valves in adults in the United Kingdom in 1990

	Cardiac units	*Numbers*	*Death*	*Complication*
Pulmonary	10	16	0	0
Aortic	16	60	7	3
Mitral	20	213	2	5
Coarction of aorta	2	6	0	1
Miscellaneous	9	14	0	0

Table 11 Paediatric interventional procedures in the United Kingdom in 1990

Procedure	*Cardiac units*	*Number*	*Death*	*Complications*
Pulmonary valve dilatation	21	258	3	0
Aortic valve dilatation	14	96	9	2
Mitral valve dilatation	2	2	0	0
Coarction of aorta	12	93	2	2
Closure of Patent ductus arteriosus	12	159	0	4
Pulmonary artery or branch stenosis dilatation	8	33	0	0
Mustard/Senning/caval dilatation	8	23	0	0
Shunt dilatation	3	7	0	0
Fallot's tetralogy	6	40	0	0
Embolisation	9	24	0	0
Subaortic stenosis	2	6	0	0
Retrieval	5	7	0	0
Blade septostomy	6	11	1	0
Closure of ventricular septal defect	1	3	0	0
Miscellaneous	2	5	0	0

coronary artery bypass grafting and the myocardial infarction rate remained much the same over these years. This increased mortality risk may be the result of more complicated cases, being attempted—such as less favourable lesions in one artery in patients with multivessel disease—rather than low risk lesions in patients with single vessel disease.

Thirteen percent of diagnostic angiograms later led to a coronary angioplasty procedure. This figure suggests that for the number of angioplasty procedures to rise to levels comparable to other countries in Western Europe—that is to 350–400 per million—it will be necessary to increase the number of diagnostic angiograms as well as the funding for coronary angioplasty.

Paediatric interventional procedures increased in number and range and maintained their low mortality and morbidity.

The British Cardiovascular Intervention Society is grateful to the staff who compiled the data requested from each cardiac unit. The adult cardiology units that took part in the 1990 survey are the same as those listed in the 1989 survey[2] with the exception that the National Heart and the Brompton Hospitals have combined (as the Royal Brompton National Heart and Lung Hospital) and the Victoria Infirmary Glasgow did not provide any information. The paediatric Cardiology units are shown below.

Paediatric cardiac units surveyed in 1990
Belfast Royal Victoria Hospital, Birmingham Children's Hospital, Bristol Royal Children's Hospital, Edinburgh Royal Hospital for Sick Children, Glasgow Royal Children's Hospital, Great Ormond Street, Guy's Hospital, Hammersmith Hospital, Harefield Hospital, Humana Wellington Hospital, Leeds Killingbeck Hospital, Leicester Groby Road Hospital, Liverpool Royal Children's Hospital, Manchester Royal Children's Hospital, Newcastle Freeman Hospital, Oxford John Radcliffe, Royal Brompton National Heart and Lung Hospital, Royal Free Hospital, Sheffield Northern General Hospital, Southampton General Hospital, St Thomas's Hospital.

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Br Heart J 1992;**68**:437–9

BRITISH CARDIAC SOCIETY

Guidelines for training in percutaneous transluminal coronary angioplasty (PTCA)

Report of the Council of the British Cardiovascular Intervention Society (BCIS)

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Coronary heart disease is responsible for considerable morbidity and is the single most common cause of death in the United Kingdom. Coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) are of proven symptomatic benefit, and CABG improves prognosis in certain subgroups of patients. As preventive measures become more widely accepted the incidence of ischaemic heart disease may decrease but despite such a decrease the demand for revascularisation procedures (CABG or PTCA) will continue to rise for the foreseeable future. There are several reasons for this: the provision of cardiological services at district level is slowly improving, more patients are surviving myocardial infarction because of the use of thrombolytic agents, and there is increasing awareness of the benefits of revascularisation procedures. With advances in technology and operator experience the results of PTCA have improved, allowing more complex coronary artery disease to be treated in this way. Finally, as the number of patients who have had revascularisation procedures in the past increases, so the number potentially requiring re-investigation for recurrent symptoms will rise in the future.

Factors such as these will increase the number of referrals to centres providing revascularisation procedures and for this demand to be met an adequate number of PTCA operators must be trained.[1] PTCA is a skilled procedure with success, failure, and complications relating to the operator's expertise and judgement and it is therefore essential that those wishing to undertake angioplasty are properly trained. This article provides guidelines aimed at optimising such training. As with other aspects of medicine it is the responsibility of all doctors performing PTCA, and particularly those training others in the technique, to ensure that in their institution the procedure can be performed safely and with a high likelihood of success.

Angioplasty training

In the United States the American Heart Association (AHA) and American College of Cardiology (ACC) have issued a joint report[2] giving clear guidelines on the training required for an individual to perform angioplasty, the facilities a centre should have, and the workload a centre should undertake before a PTCA programme can be recognised. There are many differences in medical training and practice between the United Kingdom and the United States but the American guidelines provide a useful basis for our own recommendations.

THE TRAINEE

Before being accepted for PTCA training a doctor should have a sound basic training in general (internal) medicine, hold the MRCP, and have particular experience in managing patients with ischaemic heart disease. Guidelines for cardiological training in the United Kingdom[3] and United States[4] have been clearly defined. Prospective trainees must also be proficient in pacing procedures and cardiopulmonary resuscitation and have a thorough knowledge of the use of cardiovascular drugs. These requirements mean that angioplasty trainees will usually be junior cardiologists. Radiologists who intend to pursue careers in interventional catheterisation must have received training in, and be able to manage competently, the recognised cardiological complications of PTCA and it is the responsibility of those undertaking the training of such individuals to ensure that this minimum requirement is met.

Before being accepted for PTCA training all prospective trainees should be competent to perform right and left heart catheterisation and angiography and should have undertaken at least 300 unsupervised diagnostic coronary arteriograms. Before beginning training in PTCA the trainee must be able to perform and interpret coronary arteriograms safely and without assistance. All procedures undertaken should be recorded in a log-book and countersigned by a consultant experienced in catheterisation. Individuals should be accepted for angioplasty training by the consultant(s) who will subsequently take responsibility for training and who should ensure that the prospective trainee has fulfilled the general training requirements outlined above.

THE TRAINING

The training programme should ensure that the trainee becomes competent to assess the suitability of patients for PTCA. This assessment will inevitably vary to some extent between centres and will change with new developments in the technique. Rigid criteria for case selection are inappropriate but the recommendations of the ACC/AHA Task

Force Report may be used as guidelines.[2] The trainee must be familiar with the catheter laboratory and angioplasty equipment and understand the radiation implications of PTCA procedures and the means by which radiation exposure may be minimised. In addition, there should be a clear regimen for drug therapy before, during, and after angioplasty, however much this may be based on empirical grounds.

To a large extent the training programme is an apprenticeship and should aim to expose the trainee to as wide a variety of angioplasty experience as possible. Such an approach will ensure that the complications of angioplasty and their management become familiar to the operator.

In addition to performing PTCA effectively the trainee should be directly involved in the subsequent care of patients on the ward and after discharge from hospital, the assessment of an individual's outcome after the procedure, and the auditing of results for the centre as a whole. Trainees must keep abreast of the published reports on PTCA and should be allowed sufficient time to attend meetings. Each year a minimum of four days should be spent at meetings related to angioplasty in the United Kingdom or abroad.

Defining the minimum number of PTCA procedures that constitutes an acceptable training in angioplasty is difficult because individuals learn at different rates, case selection and available facilities will differ between centres, and the number of PTCA procedures performed annually in the United Kingdom means that some centres still have a relatively small workload. From figures supplied to the British Cardiovascular Intervention Society 21 (49%) of the 43 NHS centres in the United Kingdom performed fewer than 150 angioplasties in 1990.[5] The recommendations of the AHA/ACC Task Force in the United States,[2] and those of the Joint International Society and Federation of Cardiology/World Health Organisation Task Force,[6] published in 1988, were that a minimum of 125 coronary angioplasty procedures are required, including 75 performed as a primary operator, before the individual is accredited as an independent operator. In a recent review of coronary angioplasty in the United Kingdom[7] it was suggested that 50 procedures be performed before the trainee acts as a primary operator and that after this number has been attained an experienced angioplasty operator should be available nearby to advise and if necessary take over the procedure in case of difficulty. The number of these supervised procedures that are required before a trainee is regarded as a fully independent operator was not specified. The British Cardiovascular Intervention Society recommends that trainees in the United Kingdom be involved in 100 angioplasty procedures and be the primary operator on at least 50 of these, before they can be regarded as independent operators. All procedures and their outcome should be recorded in a log-book and certified by a recognised trainer.

THE TRAINERS

By now the experience gained by consultar who have trained themselves in angioplas should be sufficient for all regional centres have at least two consultants capable of trainir junior staff in angioplasty, thus ensuring co tinuity of services when one consultant absent. The onus is on the trainer to provi adequate training and to ensure that th programme meets the requirements of bo trainer and trainee. To maintain certification a trainer in the United States requires a individual to perform at least 50 PTC procedures per year as a principal operator The British Cardiovascular Society makes th same recommendation for trainers in th United Kingdom.

TRAINING CENTRES

If one assumes that each centre has at least tw principal operators and that each requires 5 PTCA cases per year to maintain experience each training centre should undertake a minimum of 150 PTCA procedures each year if one trainee is to be trained as a primary operator. This allows 50 procedures to be undertaken by the trainee. At least 50 additional cases will be required if a second primary operator is to be trained. If trainers undertake some of their PTCA procedures in another institution the total required of the training centre may be slightly less.

The absence of on-site facilities for cardiac surgery is regarded as an absolute contraindication to PTCA in the United States[2] but has been the subject of active debate in the United Kingdom.[8 9] The British Cardiovascular Intervention Society regards on-site surgery as the strongly preferred option though it recognises that PTCA has been and can be performed satisfactorily without on-site surgery. However, units without surgery on-site must be able to demonstrate that there are formal arrangements for the prompt transfer of a patient to an operating theatre in an ambulance with staff and equipment that allow cardiac resuscitation and support.[10] A centre without surgery on-site that satisfies these requirements and performs more than 150 PTCA procedures per year may be recognised for training. However, centres with on-site surgery may offer additional experience to the trainee. The presence of surgery on-site will ensure that the widest possible range of patients will be treated in the unit and thus the trainee will be exposed to angioplasty of a wide variety of lesions. It is important that a trainee has first hand experience of patients requiring emergency surgery during angioplasty so that he/she knows when to refer a patient and that he/she is involved in care right up to the time the patient enters the operating theatre. Also, easy availability of surgical colleagues for discussion about patients before angioplasty will help the trainee make informed and sensible decisions about the most suitable form of revascularisation procedure for individual patients. Whether cardiac surgery is on or off site there should be regular discussions between PTCA operators, especially those in training, and cardiac surgeons.

Any catheter laboratory undertaking angioplasty training should be equipped with a physiological measurement system, facilities for cardiopulmonary resuscitation, and a full range of angioplasty hardware. High quality *x* ray imaging equipment capable of multiple views, including cranial and caudal angulations, should be available. Image freeze-frame and replay facilities must be instantly available. Because hard-copy images may need to be reviewed before the end of an angioplasty procedure rapid development of cineangiogram films should be possible. All centres undertaking angioplasty should provide good radiation protection for operators and catheter laboratory staff as well as patients. Centres should audit their angioplasty experiences so that results can be reviewed within their departments and accurate national data can be registered centrally with the United Kingdom Angioplasty Registry of the British Cardiovascular Intervention Society.

Conclusion

The British Cardiovascular Intervention Society makes the following recommendations for training in coronary angioplasty.

1 The trainee must have experience in general (internal) and cardiovascular medicine, and have performed and interpreted at least 300 unsupervised diagnostic coronary arteriograms before undertaking PTCA training.

2 The trainee should record diagnostic catheter procedures and PTCA procedures in a logbook.

3 The trainee must undertake at least 100 PTCA procedures, 50 of which must be as first operator, before being regarded as an independent operator.

4 Trainees should be trained in the selection of patients for PTCA and in their management after the procedure.

5 Training programmes should allow regular access to cardiac surgeons for discussion about the most appropriate form of revascularisation for individual patients.

6 A trainer should perform at least 50 PTCA procedures each year.

7 A training centre should undertake at least 100–150 PTCA procedures a year.

8 All centres undertaking PTCA should audit their procedures and are encouraged to contribute to the United Kingdom Angioplasty Registry held by the British Cardiovascular Intervention Society.

The recommendations made in this article are guidelines for establishing recognised training posts in coronary angioplasty in the United Kingdom. Since the competence of angioplasty operators, whether trainer or trainee, is to a large extent dependent on the number of procedures performed, the recommended numbers quoted should be regarded as an absolute minimum. The recommendations made are those of the Council of the British Cardiovascular Intervention Society and were discussed and accepted at the Edinburgh meeting of the Society in October 1989. They may require modification in future, in the light of further experience in the practice of coronary intervention procedures.

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Br Heart J 1992;68:440

BRITISH CARDIAC SOCIETY NEWSLETTER

Surveys: The Past

We began our surveys in cardiology in 1979 after a decision taken at the Cardiology Committee of the Royal College of Physicians, then chaired by John Goodwin. From the outset the British Cardiac Society played a leading role, using facilities provided by the University of Sussex. The first publication was in 1981, with a paper entitled "Career prospects in cardiology in England and Wales. Survey of 15 health regions". This reflected the major priority at the time, which was the plight of large numbers of time expired senior registrars. Our specialty was the first to start regular surveys and probably the first to make a determined effort to match numbers of trainees at senior registrar level to consultant vacancies. By the time the joint planning advisory committee (JPAC) came into existence we had already succeeded in this objective, and some posts in larger centres had been given up as a result of negotiation. The numbers of senior registrars becoming time expired fell progressively, but now the pendulum has swung to the point at which we are entering a period of shortage that will become acute from 1997. The Department of Health were given this information formally two years ago at a meeting between three representatives of the manpower division and two representatives of our own training and manpower group—one of whom was Peter Sleight as chairman of our Specialist Advisory Committee (SAC). No action was taken as a result of this meeting, and our application for an early JPAC review was rejected—our next opportunity was to be December 1993, too late to prevent a major crisis. But we have already alluded to the changes that have taken place within the manpower division of the Department of Health, with the complete and welcome acceptance now of cooperation rather than confrontation. As a result we *do* have an early JPAC review. The process has started and culminates with a meeting with the full committee on 19 November. We hope that the evidence we present will persuade the committee that an increase in senior registrars is appropriate.

Surveys: The Present

We suggest that some colleagues may not appreciate fully the importance of reliable manpower data in discussions that take place (frequently these days) with regional health authorities, with the Department of Health, with JPAC, and with the Colleges. We know that surveys are irksome, but they provide the ammunition we need, and without that ammunition we are near powerless. The first stage of the 1991 survey was completed by regional contacts, who are efficient and very swift in their responses. But we prefer to collect detailed information—some of which is confidential—on an individual basis. Of 443 survey forms sent out in January 1992 to confirm and supplement information already collected from our regional contacts, 82% had been returned within six weeks. After sending one reminder we still had 5% outstanding by mid May. After a second written reminder and several telephone calls 1·5% had not sent us information as late as mid June. Moreover 35 forms were completed incorrectly and had to be returned, and many of these were slow in arriving back. We always achieve 100% compliance in the end, but only in late July 1992 could work start on the 1991 returns. The forms on staffing are very simple and take only minutes to complete. The amount of effort required to collect accurate, consistent, and verified information seems unnecessarily disproportionate as well as expensive for the Society.

We have made a slight change in our classification of cardiologists for the 1991 survey. In the past, we distinguished those who did cardiology exclusively from those who also had additional responsibility for some general internal medicine. The latter group comprised only those physicians with a special interest in the specialty who had appropriate training, and who spent a minimum of 40% of their time devoted to it. (Without these criteria we do not believe it is appropriate to be called a cardiologist). The alteration relates not to these but to the first category. There are many whose working life is devoted *almost* exclusively to cardiology, but who continue to have responsibility for emergency medical admissions. Some cardiologists with "take" duties are interventionalists. It is unrealistic to classify such colleagues as anything but fully committed specialists. The division now is between individuals with a 40%+ commitment, and those with an 80%+ commitment. In other words, the exclusive cardiology group have been joined by a near-exclusive cardiology group who share the on-call commitment to general medicine. This change will distort slightly any comparison with previous years, but overall numbers will not be affected.

Surveys: The Future

Cardiologists—and other members of specialist groups—have been at risk of receiving forms from two different manpower surveys that seek very similar information, because the Royal College of Physicians now conducts its own overview surveys and does so very efficiently. Duplication of effort is irritating for all concerned, and Professor Steven Semple has agreed that the British Cardiac Society can be responsible for data collection from all cardiologists on our own lists. We prefer to collect our own speciality data for several reasons. First, our system is now well refined and works well. Secondly our numbers are relatively small so that most individuals are known to us and all data can be carefully verified. Thirdly and most importantly we can use our own criteria for defining who should be counted as a cardiologist whereas the College has to depend on other opinions that may be inaccurate and inconsistent. There has been a tendency for College numbers to be lower than our own because some cardiologists (even in major centres) have been counted as physicians. The Department of Health now pays close attention to College data (which is accurate overall if not by specialty), and in consequence the calculation for cardiology senior registrar numbers could be distorted. By using a comon data set any ambiguities over specialist responsibility will be removed. We will send out the College's own excellent forms with a supplementary sheet for the additional data that we require. Other specialties may decide to follow this lead in future. We are sure you will approve of this arrangement on the grounds both of efficiency and accuracy. We are grateful to the College manpower office for their cooperation and trust. In future index dates will always be September which is the month always chosen by the Department of Health.

News from Europe

Philip Poole-Wilson writes: "The European Society of Cardiology is made up of 32 national societies and 24 working groups. You might wish to know who in Britain represents British interests within the European Society. At present we have strong representation. Each of the 24 working groups has two chairmen making a total of 48 persons. At present no less than nine come from the United Kingdom. They are: Robert Anderson, developmental anatomy and pathology; John Camm, arrhythmias; Henry Dargie, exercise physiology; Andrew Henderson, pathogenesis of atherosclerosis; Colin Prentice, thrombosis and platelets; Anthony Rickards, cardiac pacing; Peter Sleight, hypertension and the heart; Jane Somerville, grown-up congenital heart disease; Ann Townsend, cardiovascular nursing.

We also have substantial representation on the administration side. Raphael Balcon is the representative of the working groups on the advisory board of the European Cardiology Congress Organisation (ECCO). Andrew Henderson is a member of the research fellowship and training committee which determines the 12 awards that are given annually. Philip Poole-Wilson is the secretary of the Society. Peter Sever is on the executive scientific committee that has overall responsibility for organising the final programme for the annual congress. Peter Sleight is on the nominating committee that puts forward names for future boards. In addition, we have two representatives on the monospecialty in cardiology in the European Union of Specialist Doctors (UEMS): Michael Petch was appointed by the British Cardiac Society and John Martin was appointed by the British Medical Association after nomination by the Royal College of Physicians.

News of colleagues

Howard McAlpine has been appointed as physician and cardiologist at the Victoria Infirmary Glasgow, and Graham Stuart as paediatric cardiologist at the University Hospital of Wales. We are very pleased to know that Raphael Balcon is the new chairman of the cardiology committee of the Royal College of Physicians, and under a recent change in our constitution becomes an ex officio member of Council of the British Cardiac Society. We were also delighted to hear recently of a new honour bestowed upon John Goodwin. He has been awarded the Enzo Ferrari Prize in Cardiology by the Ferrari Trust (Premio Ingenier Enzo Ferrari) of Modena, Italy. The prize is relatively new. Previous winners have been Eugene Braunwald and John Ross. The recipient is requested by the Foundation to give a lecture. John will be travelling to Italy to speak on 19 October on "Diastolic Heart Disease".

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
DUNCAN DYMOND
Secretary, British Cardiac Society,
9 Fitzroy Square,
London W1P 5AH

NOTICE

The 1993 Annual Meeting of the **British Cardiac Society** will take place at the Wembley Conference Centre from 18 to 21 May.

THIRD INTERNATIONAL SYMPOSIUM ON ACE INHIBITION

RAI CONGRESS CENTRE, AMSTERDAM, THE NETHERLANDS, 19–23 MARCH 1993

Under the auspices of the ISAG (International Scientific Academic Group on the renin-angiotensin system and its inhibition), it is the aim of the Organising and Scientific Committee to run the Third International Symposium along similar lines to the two highly successful meetings held in London in 1989 and 1991.

Contemporary issues relating to ACE inhibitors and their use will be discussed, together with consideration of new areas of research and therapy. Invited lectures by distinguished speakers, free communications based on refereed abstracts, poster presentations and satellite symposia will be included to assess the role of ACE inhibitors and their applications for the practising Clinician.

Topics for discussion include:

- **ACE inhibitors in hypertension**
- **ACE inhibitors and the progression of renal disease**
- **ACE inhibitors and diabetes**
- **Growth effects of ACE inhibitors**
- **Molecular biology and biochemistry of ACE inhibitors**
- **Heart failure and ACE inhibitors**
- **Tissue renin systems**
- **Renin inhibitors and angiotensin II antagonists**
- **ACE inhibitors, quality of life, mood and cognition**
- **Economics of cardiovascular health care**
- **Circulating *vs.* tissue renin**
- **ACE inhibitors and myocardial salvage**

DEADLINE FOR RECEIPT OF ABSTRACTS: 30 OCTOBER 1992

Further information, registration and abstract forms can be obtained from:
Professor G.A. MacGregor and Professor P.S. Sever, Organising and Scientific Committee
Third International Symposium on ACE Inhibition
c/o Ian Shepherd
ISAG, The Old Ribbon Mill, Pitt Street, Macclesfield, Cheshire SK11 7PT, UK
Tel: (44) (0)625 618507. Fax: (44) (0)625 610260. Telex: 665328 GCCG

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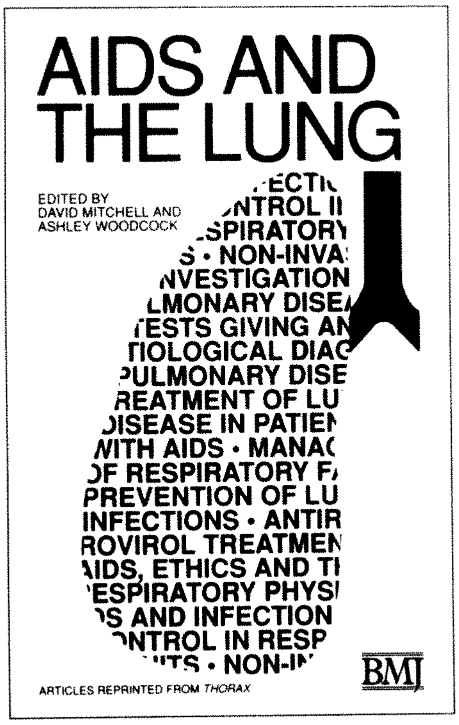

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The length of time a patient's BP is 'in the red' (>140/90 awake, 120/80 asleep) is known as 'BP load'[1]. It is linked to the prevalence of left ventricular hypertrophy – a strong predictor of cardiovascular morbidity and mortality[2].

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Congestive heart failure: Adults (including elderly): initially 2.5mg daily in hospital under close medical supervision, increasing to 5-20mg once-daily according to response. Monitor blood pressure and renal function.

Renal impairment: May require lower maintenance dosage.

CONTRAINDICATIONS: Pregnancy. Hypersensitivity to 'Zestril'. Patients with history of angioneurotic oedema to previous ACE inhibitor therapy. Patients with aortic stenosis, cor pulmonale or outflow tract obstruction.

PRECAUTIONS: Assessment of renal function is recommended. Symptomatic hypotension may occur, particularly in volume depleted patients and congestive heart failure. Caution in patients with ischaemic heart or cerebrovascular disease; renal insufficiency; renovascular hypertension. Patients with a history of angioedema may be at increased risk of angioedema with an ACE inhibitor. Cough has been reported with ACE inhibitors. Renal impairment (usually reversible) may occur in some patients. Hypotension may occur during surgery or anaesthesia. Caution in nursing mothers. No paediatric experience. Afro-Caribbean patients may show reduced therapeutic response. Symptomatic hypotension can be minimised by discontinuing diuretic prior to 'Zestril'. Interaction with indomethacin and lithium. Potassium supplements, potassium sparing diuretics and potassium containing salt substitutes not recommended. Avoid concomitant use with high-flux dialysis membranes.

SIDE EFFECTS: Hypotension, dizziness, headache, diarrhoea, cough, nausea, fatigue. Less frequently, rash, asthenia. Rarely, angioneurotic oedema and other hypersensitivity reactions, myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients, palpitation, tachycardia, abdominal pain, dry mouth, hepatitis, jaundice, mood alterations, mental confusion, urticaria, diaphoresis, uraemia, oliguria/anuria, renal dysfunction, acute renal failure, impotence. A symptom complex which may include fever, vasculitis, myalgia, arthralgia/arthritis, positive ANA, elevated ESR, eosinophilia, leukocytosis; rash, photosensitivity or other dermatological manifestations may occur. Increases (usually reversible) in blood urea, serum creatinine, liver enzymes and serum bilirubin. Decreases in haemoglobin and haematocrit have occurred. Hyperkalaemia.

PRODUCT LICENCE NUMBERS AND BASIC NHS COSTS: 'Zestril' 2.5mg (29/0208) 28 tablets, £7.84; 5mg (29/0204) 28 tablets, £9.83; 10mg (29/0205) 28 tablets, £12.13; 20mg (29/0206) 28 tablets, £13.72.

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Further information is available from: ICI Pharmaceuticals, King's Court, Water Lane, Wilmslow, Cheshire SK9 5AZ.

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Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, 9 Fitzroy Square, London W1P 5AH, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;**296**:401–5). **Authors are asked to complete a copy of the checklist provided (1992;67:118–9 (January issue)) when submitting their manuscripts for publication.** The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with wide margins.)

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CASE REPORTS should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

ABBREVIATIONS should *not* be used in the text, except for mathematical calculations and units of measurement.

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Figure legends must include an explanation of all abbreviations used in the Figure.

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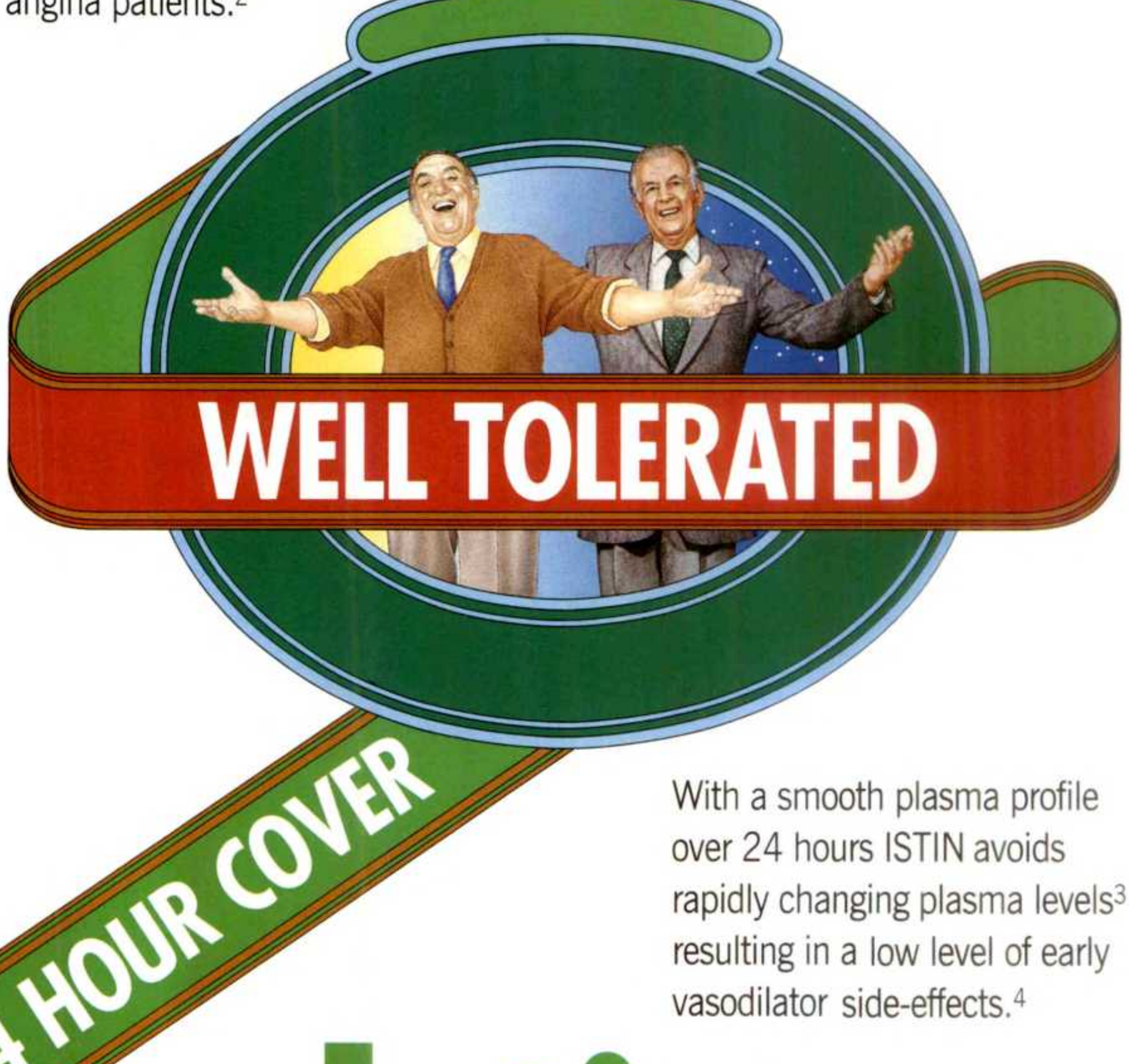
ISTIN is a once daily calcium antagonist that controls blood pressure for a full 24 hours.[1]

Additionally, ISTIN provides full 24 hour cover for your angina patients.[2]



With a smooth plasma profile over 24 hours ISTIN avoids rapidly changing plasma levels[3] resulting in a low level of early vasodilator side-effects.[4]

Istin*

AMLODIPINE

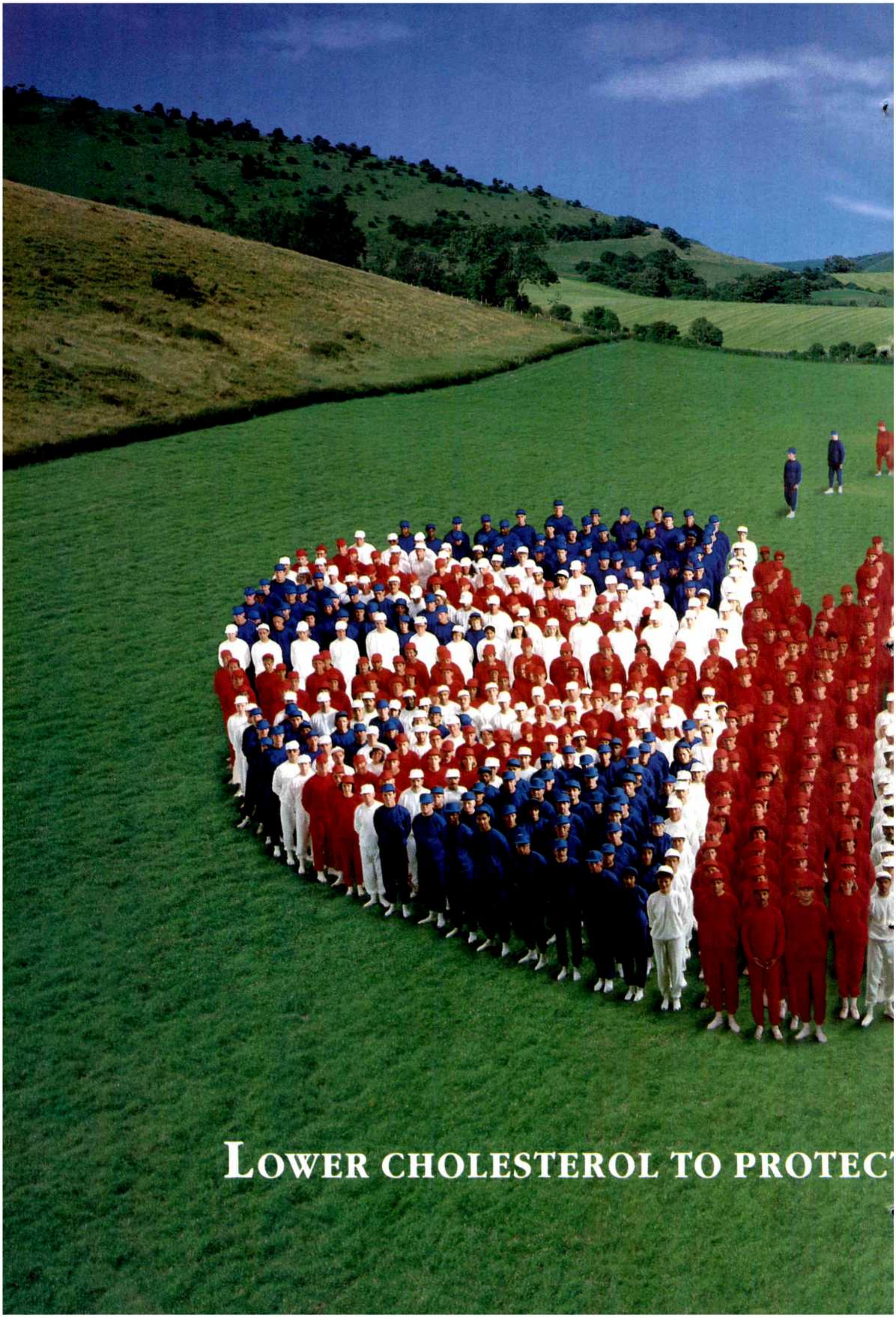
A USER FRIENDLY CALCIUM ANTAGONIST

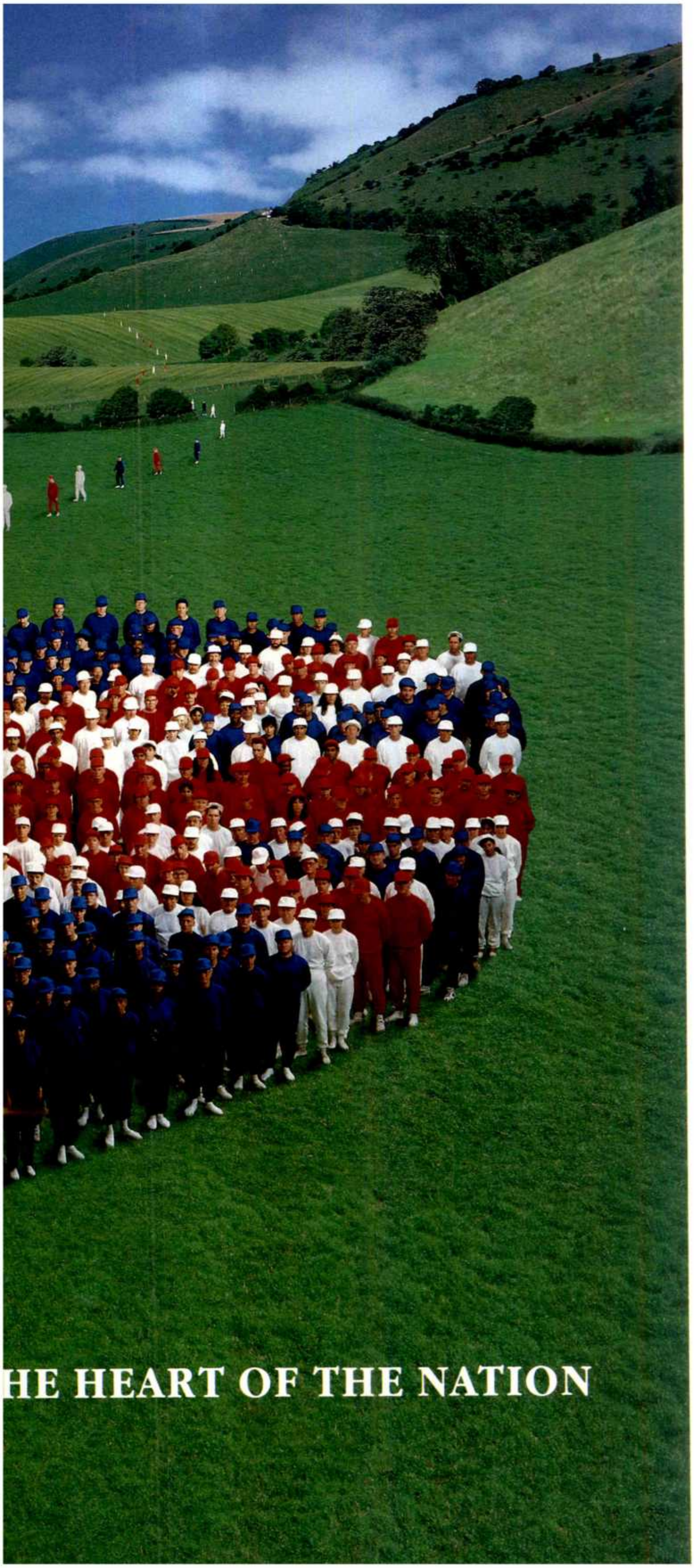
ABBREVIATED PRESCRIBING INFORMATION FOR ISTIN*. INDICATIONS: FIRST-LINE TREATMENT OF HYPERTENSION AND MYOCARDIAL ISCHAEMIA ASSOCIATED WITH STABLE ANGINA PECTORIS OR VASOSPASTIC (PRINZMETAL'S OR VARIANT) ANGINA. **DOSAGE:** FOR HYPERTENSION AND ANGINA, INITIAL DOSAGE 5MG ORALLY ONCE DAILY WHICH MAY BE INCREASED TO A MAXIMUM DAILY DOSAGE OF 10MG. **USE IN CHILDREN:** NOT RECOMMENDED. **USE IN THE ELDERLY:** NORMAL DOSAGE. **USE IN RENAL IMPAIRMENT:** NORMAL DOSAGE. **USE IN HEPATIC IMPAIRMENT:** DOSAGE RECOMMENDATIONS HAVE NOT BEEN ESTABLISHED; USE WITH CAUTION. **CONTRA-INDICATIONS:** KNOWN SENSITIVITY TO DIHYDROPYRIDINES. **WARNINGS AND PRECAUTIONS:** PREGNANCY AND LACTATION: ISTIN SHOULD NOT BE ADMINISTERED DURING PREGNANCY OR LACTATION, OR TO WOMEN OF CHILD-BEARING POTENTIAL UNLESS EFFECTIVE CONTRACEPTION IS USED. **SIDE-EFFECTS:** HEADACHE, OEDEMA, FATIGUE, NAUSEA, FLUSHING, AND DIZZINESS. **PACKAGE QUANTITIES AND BASIC NHS COST:** 5MG TABLETS CALENDAR PACK OF 28 £11.85 (PL 0057/0297); 10MG TABLETS CALENDAR PACK OF 28 £17.70 (PL 0057/0298). FURTHER INFORMATION ON REQUEST. **PFIZER LIMITED**, SANDWICH, KENT. **REFERENCES:** **1.** MROCZEK WJ, BURRIS JF AND ALLENBY KS, J CARDIOVASC PHARMACOL, 1988, **12** (SUPPL 7): S79-S84. **2.** TAYLOR CR ET AL, PRESENTED AT A SYMPOSIUM ON CIRCADIAN VARIATION IN CARDIOVASCULAR DISEASE: THE NEED FOR COMPLIANCE, SEPTEMBER 1990. **3.** DATA ON FILE: PFIZER PROTOCOL 368. **4.** OSTERLOH I, AM HEART J, 1989, **118**: 1114-1120.

*Trade Mark

Pfizer

60580


LOWER CHOLESTEROL TO PROTEC


HE HEART OF THE NATION

- In 1989, coronary heart disease caused 26% of all deaths in England, Wales, and Scotland![1]
- 1% reduction in cholesterol reduces coronary heart disease by 2%![2]
- The EAS/BHA goal of treatment: <5.2 mmol/l.
- 'Zocor' is indicated in patients with primary hypercholesterolaemia with a cholesterol level of 6.5 mmol/l or greater and resistant to dietary control.

THE 1991
UK PRIX GALIEN
SPECIAL COMMENDATION

ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

INDICATIONS Primary hypercholesterolaemia unresponsive to diet with a cholesterol level of 6.5 mmol/litre or greater.

DOSAGE AND ADMINISTRATION Initially 10 mg *nocte*: dose range 10-40 mg once daily *nocte*. Maximum therapeutic response occurs within four to six weeks. Consider dose reduction if total serum cholesterol level falls below 3.6 mmol/l or if LDL cholesterol falls below 1.94 mmol/l. (See Data Sheet for full dosage instructions.) A standard cholesterol-lowering diet should be continued. *Concomitant therapy:* 'Zocor' is effective alone or in combination with bile-acid sequestrants. Lowest recommended dose should be used with immunosuppressants. *Impaired renal function and elderly patients:* Modification of dose should not be necessary. *Children:* Studies to show safety and efficacy have not been done.

CONTRA-INDICATIONS Hypersensitivity to this product; active liver disease or unexplained persistent elevations of serum transaminases; pregnancy and breast-feeding; women of child-bearing potential unless adequately protected by non-hormonal methods.

PRECAUTIONS *Homozygous familial hypercholesterolaemia:* 'Zocor' is unlikely to be effective. *Hypertriglyceridaemia:* 'Zocor' is not indicated where hypertriglyceridaemia is the abnormality of most concern. *Hepatic effects:* Initial and periodic liver function monitoring recommended. Discontinue if persistent enzyme elevations occur, particularly if they rise to three times the upper limit of normal. Caution in patients with a history of liver disease and/or alcoholism. *Muscle effects:* Clinically insignificant transient mild elevations of creatine phosphokinase have been seen. Therapy with 'Zocor' should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected. *Pregnancy:* Contra-indicated. One month should elapse between ending therapy with 'Zocor' and planned conception. *Drug interactions:* Care should be taken in patients on concomitant lipid-lowering therapy, particularly fibrates or nicotinic acid derivatives or immunosuppressive therapies.

SIDE EFFECTS Side effects reported in controlled clinical trials: abdominal pain, constipation, flatulence, asthenia, and headache. Rarely, myopathy. Side effects reported either in long-term extension studies or in marketed use: nausea, diarrhoea, rash, dyspepsia; and rarely, rhabdomyolysis and hepatitis. Isolated cases of angioneurotic oedema also have been reported.

BASIC NHS COST 10 mg tablets, £18.29 for 28-tablet calendar pack. 20 mg tablets, £31.09 for 28-tablet calendar pack.

Product licence numbers: 10 mg tablets, 0025/0241.
20 mg tablets, 0025/0242. Issued December 1991.

® denotes registered trademark of Merck & Co., Inc., Rahway, NJ, USA

REFERENCES
1. OPCS Monitor DH2, June 1990.
2. Lipid Research Clinics Program. *J. Amer. med. Ass.*, 1984, **251**, 351.

Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU

MSD
MERCK SHARP & DOHME

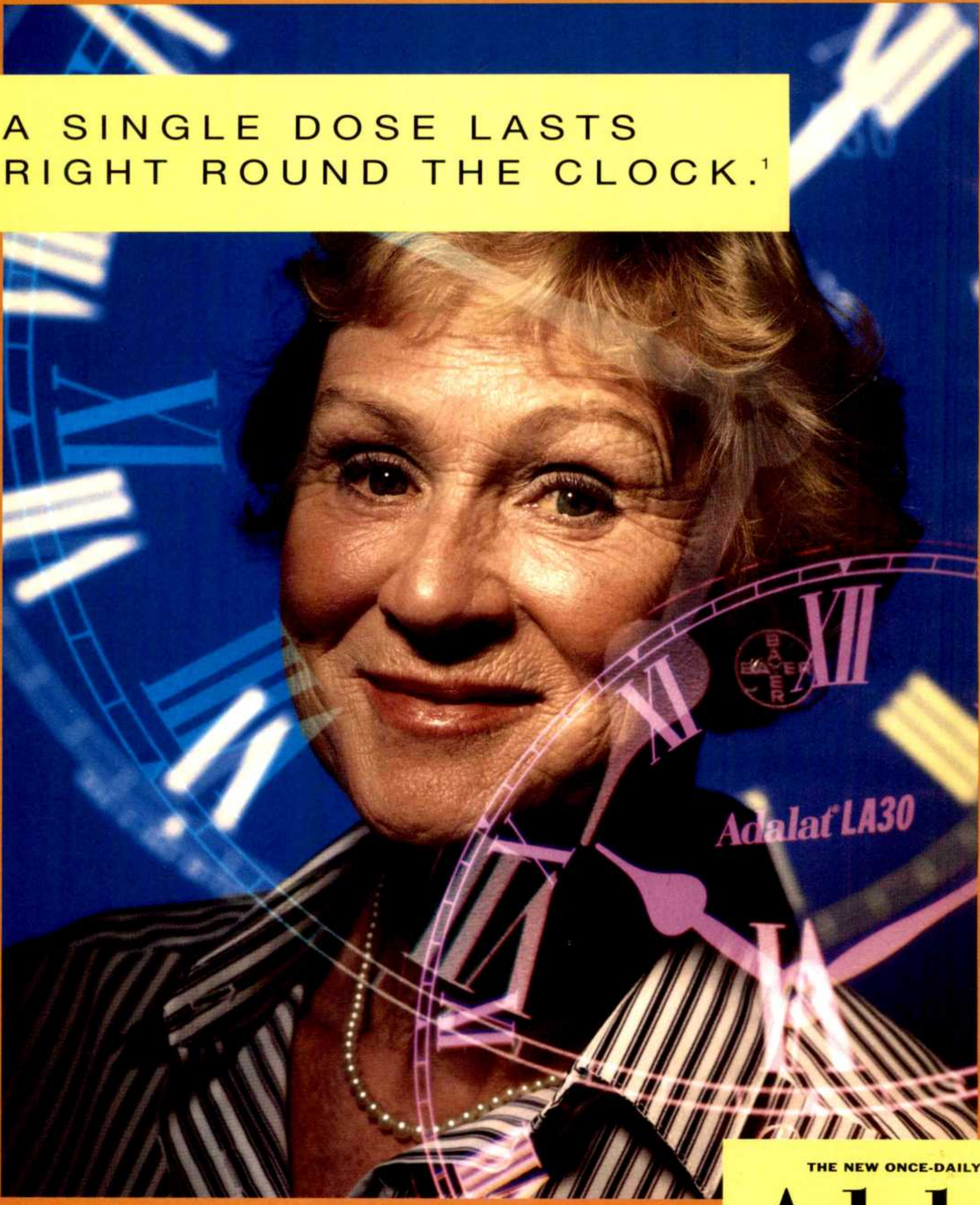
ZOCOR®

(simvastatin, MSD)

Reducing cholesterol to help prevent coronary heart disease

12-92 ZCR.91.GB.7157I.J

A SINGLE DOSE LASTS RIGHT ROUND THE CLOCK.[1]



THE NEW ONCE-DAILY

Adalat LA30

LONG ACTING

nifedipine 30m

FOR HYPERTENSION

Adalat®LA30/Adalat®LA60 ABRIDGED PRESCRIBING INFORMATION (Refer to full data sheet before prescribing) **Presentation:** Pink lacquered tablets each containing 30mg or 60mg nifedipine in a controlled release formulation, one side marked Adalat 30 or Adalat 60. **Indications:** Mild to moderate hypertension. **Dosage and Administration:** Adalat LA tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up. One 30mg tablet once daily swallowed whole with a glass of fluid to be taken at approximately 24 hour intervals, preferably during the morning. Dosage can be increased according to individual requirements up to a maximum of 90mg once daily. Patients controlled on Adalat capsules or Adalat Retard may be safely switched to Adalat LA at the recommended initial dose of 30mg once daily, with subsequent titration to a higher dose as clinically warranted. *Renal impairment* Dosage adjustment should not be necessary. *Elderly* Dosage adjustment not usually necessary. *Children* No recommendations for use. **Contra-indications, warnings etc. Contra-indications:** Known hypersensitivity to nifedipine; women of child-bearing potential and nursing mothers; hepatic impairment; history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract; inflammatory bowel disease. **Warnings and precautions:** If used in combination with beta-blocking drugs and other antihypertensives, a possible additive effect resulting in postural hypotension should be borne in mind. Adalat LA will not prevent possible rebound effects after cessation of other antihypertensive therapy. Caution in patients whose cardiac reserve is poor. If ischaemic pain is observed following the introduction of therapy, discontinue treatment. Diabetic patients may require adjustment of their control. **Interactions:** Interactions have been observed with cimetidine and quinidine. **Side-effects:** Headache, dizziness, flushing and gravitational oedema. Less common side-effects include rash, nausea, lethargy and increased frequency of micturition, hypersensitivity-type jaundice, and gingival hyperplasia which may regress on withdrawal of therapy. **Legal category:** POM. **Package Quantities and Basic NHS Cost:** Calendar packs containing 28 tablets; Adalat LA 30 £11.76, Adalat LA 60 £15.40. **Product Licence Numbers:** PL 0010/0174-0175. **Date of Preparation:** April 1992. **References: 1.** Chung M *et al. Am J Med.* 1987; **83** (Suppl 6B): 10-14. **Further information available from:** Bayer plc, Pharmaceutical Business Group, Bayer House, Strawberry Hill, Newbury, Berkshire RG13 1JA. Telephone: (0635) 39000. ® Registered trademark of Bayer AG. © Bayer plc, August 1992. Bayer and ✚ are trademarks of Bayer AG.

Bayer

British Heart J 1992;68:441–2

BRITISH
HEART
JOURNAL

Editorial

Magnesium and the myocardium

The publication of the results of the Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) produced headlines in the national press. There was a 24% relative reduction in mortality and a 25% reduction in the incidence of heart failure, benefits conferred equally on thrombolysed and non-thrombolysed patients.[1] Magnesium is clearly here to stay, but little is known of this fascinating cation despite its presence at the centre of the chlorophyll molecule and as part of the active binding site of ATPase. In humans magnesium is a physiological necessity, but it is also active pharmacologically. This has resulted in considerable confusion—particularly in the area of cardiac arrhythmia.

Cardiovascular consequences of magnesium depletion

In a classic description of magnesium deficiency, Whang and Welt described cerebral irritability with muscle tetany and ataxia in dogs.[2] Rapidly progressive hypomagnesaemia was associated with severe hypokalaemia that was resistant to treatment with potassium supplementation. Histologically there was calcification of the myocardium with pathological arterial fibrinoid changes. A progressive cardiomyopathy was seen with a rise in intracellular calcium and mitochondrial calcium deposition.[3]

In humans there was a similar picture of calcium overload associated with myocardial magnesium depletion in cardiac transplant recipients rendered (incidentally) magnesium deficient by cyclosporin.[4] Cardiac arrhythmia was not seen. In postmortem studies in ischaemic heart disease, myocardial magnesium content was up to 20% lower and calcium content up to six times higher than in non-ischaemic controls, particularly when death was sudden.[5] Myocardial potassium content was concurrently reduced. Hypomagnesaemia is an independent risk factor for patients with heart failure but it is not associated with an increased incidence of arrhythmia on Holter monitoring. Lipid profiles are adversely affected with a reduction in the HDL/LDL ratio contributing to the adverse cardiovascular profile of magnesium deficiency.

Magnesium, potassium, and cardiac arrhythmia

Myocardial magnesium depletion is associated with important intracellular potassium deficiency. Cardiac arrhythmia is well described in patients with hypomagnesaemia or myocardial magnesium depletion, or both, but in all reports magnesium imbalance was associated with concurrent hypokalaemia. This association precludes the identification of magnesium depletion as the single cause of arrhythmia. The myth surrounding magnesium depletion and cardiac arrhythmia is seen to arise from the dubious deduction that because intravenous magnesium abolishes arrhythmia in hypomagnesaemic subjects, hypomagnesaemia is therefore the cause of the arrhythmia. However, magnesium modifies ventricular tachycardia and other arrhythmias, irrespective of serum magnesium concentration, in many patients who have no reason to be magnesium deficient. Cardiac arrhythmia was not seen in the animal studies of severe magnesium depletion.

Magnesium as an antiarrhythmic agent

In 1935 Zwillinger used intravenous magnesium to treat ventricular arrhythmia associated with digoxin toxicity.[6] Since then there have been numerous case reports of the efficacy of magnesium in both supraventricular and ventricular tachycardia, albeit with an unfortunate dearth of randomised, controlled trials. Since the Cardiac Arrhythmia Suppression Trial, the benefits of a safe, cheap, "natural" drug are more readily appreciated and the use of magnesium as an antiarrhythmic agent is once again becoming popular.

Five to ten mmol of magnesium sulphate administered over a few minutes will abolish torsade de pointes (by an effect on phase 4 calcium current), reduce digoxin-associated arrhythmia (by modification of membrane digoxin kinetics), and terminate (or render pace-terminable) many sustained ventricular tachycardias. It is salutary to note that in many studies, magnesium was effective in restoring sinus rhythm when used as a "last resort" after the prior administration of a mixture of other agents.

Patch-clamp studies showed that the magnesium ion modifies at least three potassium channels, as well as acting on both L and T type calcium channels.[7] The documented electrophysiological effects of magnesium are largely confined to slowing of conduction in the atrioventricular node, but recent evidence from the denervated heart in vivo suggests that prolongation of the action potential does occurr (as predicted from in vitro studies). An increase in tachycardia cycle length was seen in clinical practice.[8] These observations strongly suggest a mode of action for magnesium as an antiarrhythmic agent and should begin to dispel the scepticism surrounding its use.

Magnesium as a calcium antagonist

Magnesium has been dubbed "nature's calcium antagonist", an effect most clearly seen in the antagonistic roles of magnesium and calcium in the determination of arterial tone. The action of endothelium relaxing factor (EDRF) is magnesium dependent and is antagonised by calcium. Spasm in angiographically normal coronary arteries was lessened or abolished by an intravenous bolus of magnesium, and there was some suggestion that hypomagnesaemia can provoke spasm.[9]

The haemodynamic effects of magnesium in vivo are largely mediated by a fall in systemic vascular resistance secondary to arteriolar vasodilatation. An intravenous bolus sufficient to double serum concentrations is cleared from the blood within 20 minutes, largely by renal excretion. Optimistic trials exploiting these effects to treat systemic hypertension with oral magnesium have met with little success—rapid clearance by the kidney prevents serum concentrations rising above normal.[10]

The use of intravenous magnesium in the acute treatment of uncontrolled pregnancy related hypertension (pre-eclampsia) is established in Australia and the United States, but for some reason has not proved popular in Europe. The intense vasoconstriction associated with this condition is particularly sensitive to the dilatatory effects of magnesium, which also acts in neurological tissue as a membrane stabiliser to reduce muscular and cerebral irritability. Indeed, the first use of magnesium in humans related to an attempt to induce "anaesthesia" in two intrepid researchers, who discovered that the illusion of anaesthesia was in fact a state of profound muscle relaxation bounding on paralysis![11]

Magnesium as an anti-ischaemic agent

Meta-analysis of several trials has suggested a beneficial role for intravenous magnesium infused in the 24 hours after acute myocardial infarction.[12] The most recent of the International Studies of Infarct Survival (ISIS 4), investigating the effects of oral nitrates and angiotensin converting enzyme inhibitors includes a similar period of intravenous magnesium administration in a $2 \times 2 \times 2$ factorial design, and will complement the results of the LIMIT-2 study.

The mechanisms of action of magnesium in this circumstance are unknown. A significant reduction in the incidence of cardiogenic shock was noted in one study, which, taken with the LIMIT-2 data, suggests that magnesium may preserve left ventricular function by reducing ischaemic damage. Evidence from animal models suggests that this may be due to reduction in calcium-mediated ischaemic damage. During ischaemia, intracellular free magnesium concentrations rise rapidly as the formation of ATP from ADP (incorporating magnesium) is limited by hypoxia and acidosis with subsequent loss of magnesium from the cell magnified by cAMP mediated β receptor stimulation.[13] During reperfusion, magnesium is re-incorporated into ATP to produce a net fall in intracellular free magnesium with reciprocal calcium overload.

In addition to any possible antiarrhythmic action, magnesium raises fibrillation thresholds; it also has antiplatelet effects mediated via prostacyclin, prolonging bleeding time.[14] The beneficial effects of magnesium on arterial tone may also be important in what will prove to be a very complex relation.

Magnesium deficiency is probably an important risk factor in cardiovascular disease that has adverse effects on arterial tone and myocardial calcium balance. The arrhythmogenic effects of hypomagnesaemia are not seen in the absence of concomitant potassium imbalance. Therapeutically, magnesium has many of the characteristics of the ideal drug—it is simple, cheap, has a wide therapeutic range, a short half-life and a limited capacity for adverse interaction with other agents. As an adjuvant antiarrhythmic agent for the acute control of ventricular tachycardia, magnesium might be considered as a first line agent. Its potential anti-ischaemic actions are becoming established in myocardial infarction, but it might also prove useful in unstable angina and in the peri and post angioplasty periods.

T A MILLANE
A J CAMM

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St George's Hospital Medical School,
London

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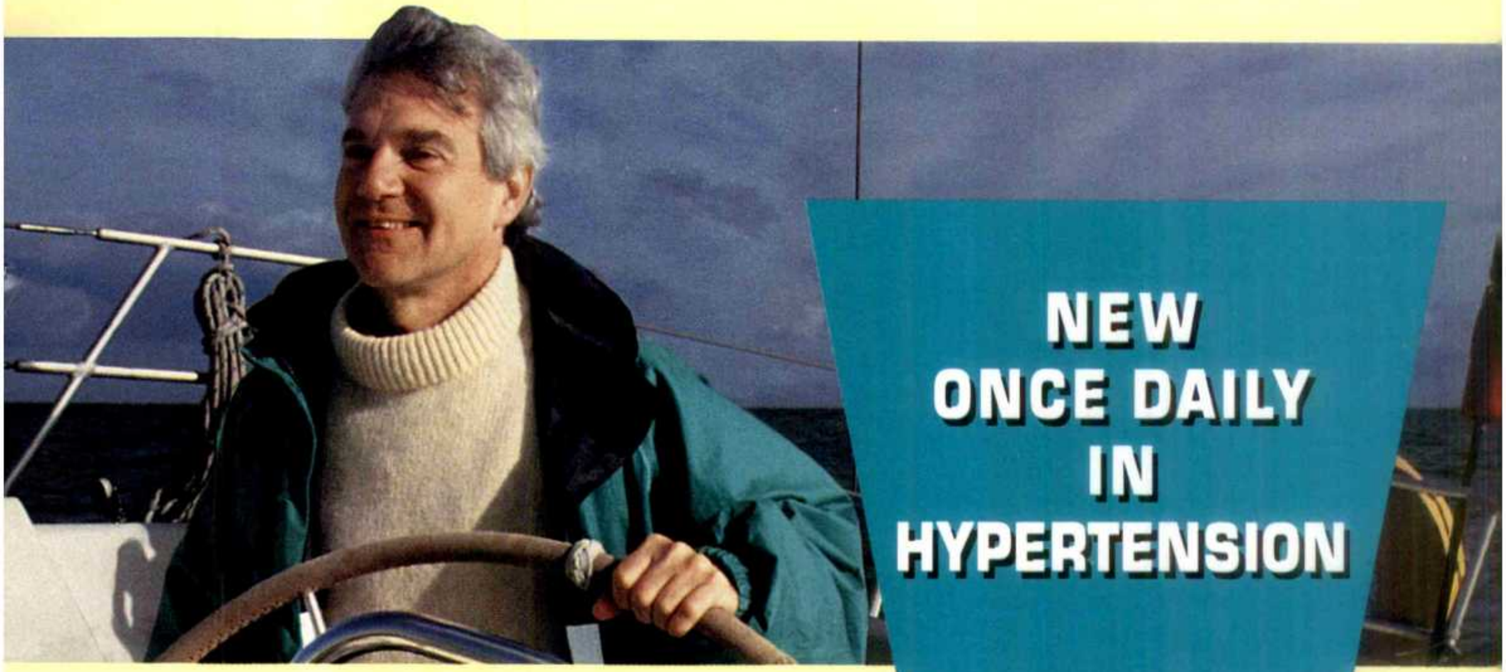
bbreviated Prescribing Information Presentation: Capsule containing 300mg diltiazem hydrochloride. **Indication:** Mild to moderate hypertension. **Dosage: Adults:** One capsule ily. **Elderly/hepatic or renal impairment:** Tildiem Retard 120mg once daily. Dose should not be increased if heart rate is below 50 beats per minute. Refer to Data Sheet for full formation. **Contraindications:** Pregnancy, women of child-bearing potential, marked bradycardia, sick sinus syndrome, left ventricular failure with stasis, second or third degree block in the absence of a pacemaker, concomitant use with dantrelone infusion. **Warnings and precautions:** Caution in patients with mild bradycardia, reduced left ventricular nction, prolonged PR interval, and during concomitant use with alpha blockers, and with beta blockers or other drugs known to induce bradycardia. (Refer to data sheet for full formation.) **Side effects:** Bradycardia, first degree heart block, headache, malaise, ankle oedema, hot flushes, gastrointestinal disturbances, palpitations, skin rash including metimes severe vascular skin reactions. **Basic NHS Cost:** 28 capsules £11.00. **Product licence number:** 4969/0014. Data sheet with full prescribing information available on quest. Tildiem and Lorex are trade marks. **References:** 1. Dupont AG, Cardiovasc Drugs Ther 1991; 5: 701-708. 2. Data on file. Lorex Pharmaceuticals d. 1992. Lorex Pharmaceuticals Ltd., P.O. Box 293, Lane End Road, High Wycombe, Bucks, HP12 4HL. Tel: (0494) 526188. TL:YAAD 102 October 1992.

LOREX



LAIN SAILING

Tildiem is a widely established cardiovascular therapy. Now, once daily Tildiem LA offers simple 24-hour control of mild to moderate hypertension.[1] Tildiem LA is an effective antihypertensive with remarkably few side-effects,[2] and should become a calcium antagonist of choice in the management of hypertension. Offering control and convenience, Tildiem LA lets your patients enjoy a full and active life.

TILDIEM® LA
ONCE DAILY
diltiazem

FOR THE LIFE OF YOUR HYPERTENSIVES

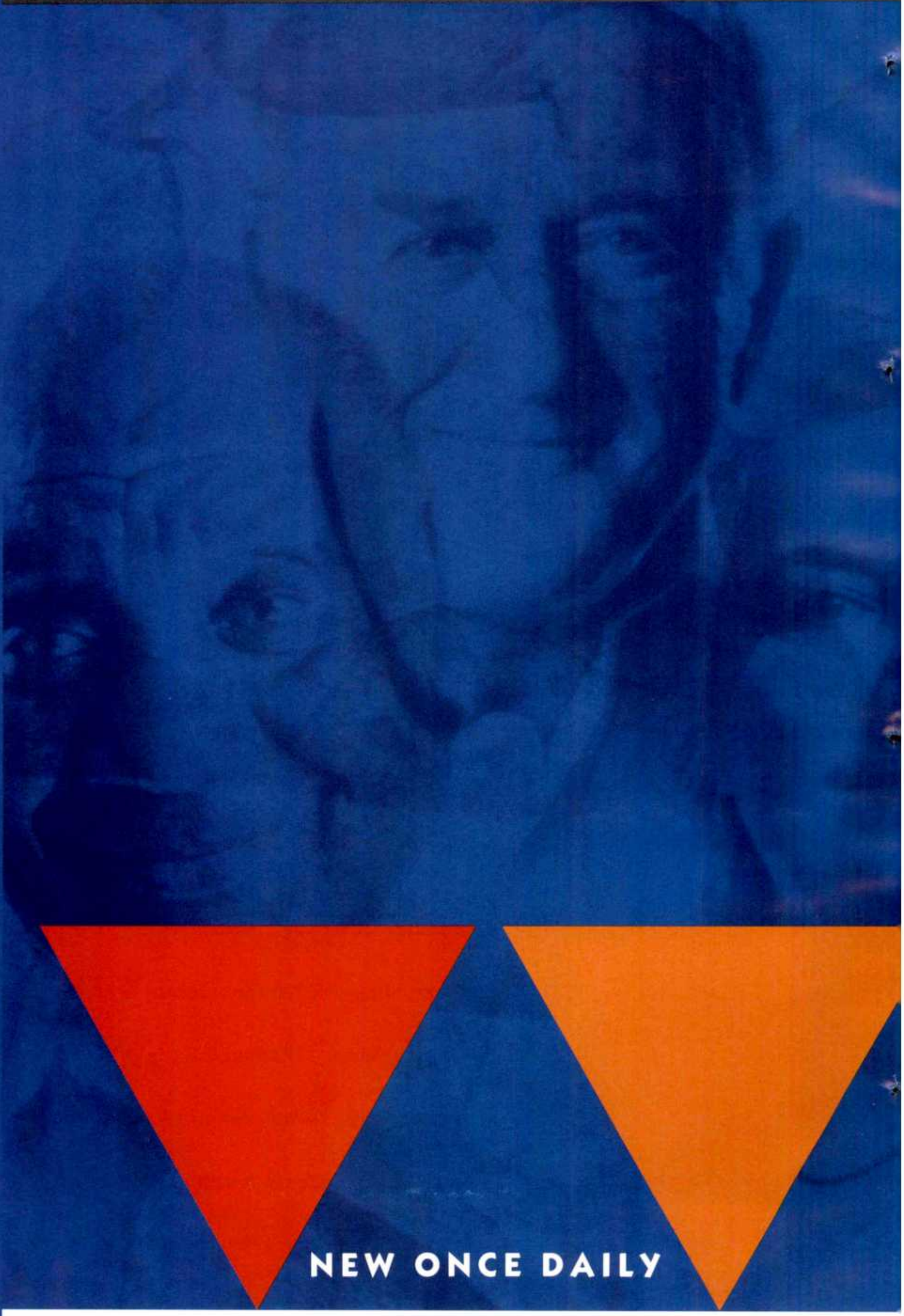
sanofi WINTHROP

ABBREVIATED PRESCRIBING INFORMATION

Presentation: White, capsule-shaped tablets marked 77T on one side with a breakline on the other, each containing 100mg ciprofibrate. **Uses:** For the treatment of primary hyperlipidaemia resistant to appropriate dietary management, including hypercholesterolaemia, hypertriglyceridaemia and combined hyperlipidaemia. In the Fredrickson classification, this includes types IIa, IIb, III and IV. **DOSAGE: Adults:** Initially one tablet (100mg ciprofibrate) per day is recommended with subsequent adjustment according to therapeutic response. The maximum dose should not exceed 2 tablets (200mg ciprofibrate) per day which may be taken as a single dose. **Elderly patients:** As for adults but see precautions and warnings. **Use in impaired renal function:** In moderate renal impairment it is recommended that dosage be reduced to one tablet every other day. Patients should be carefully monitored. MODALIM should not be used in severe renal impairment. **Use in children:** Not recommended since safety and efficacy in children have not been established. **Contra-indications:** Severe hepatic impairment, severe renal impairment, pregnancy and lactation. **Use in pregnancy and lactation:** There is no evidence that ciprofibrate is teratogenic, but there were signs of toxicity at high doses in teratogenicity tests in animals, and ciprofibrate has been shown to be excreted in breast milk in rats. In the absence of data on its use in human pregnancy or lactation, MODALIM is contraindicated during pregnancy and in nursing mothers. **Precautions:** Use with caution in patients with impaired renal or hepatic function. Abnormal liver function tests have been observed occasionally. Periodic liver function tests, including alanine amino-transferase, are recommended. MODALIM treatment should be halted if liver enzyme abnormalities persist. If, after several months therapy, serum lipid concentrations are not satisfactorily controlled, additional or different therapeutic measures should be considered. **Interactions:** Ciprofibrate is highly protein bound and therefore likely to displace other drugs from plasma protein binding sites. MODALIM has been shown to potentiate the effect of warfarin indicating that concomitant oral anticoagulant therapy should be given at reduced dosage and adjusted according to prothrombin time. Although there are no specific data, it is likely that ciprofibrate will also potentiate the action of oral hypoglycaemic agents and its action may be affected by oral contraceptives. **Side effects:** There have been occasional reports of headache, vertigo, rashes and gastrointestinal symptoms including nausea, vomiting, diarrhoea and dyspepsia. Generally these side effects were mild to moderate in nature and occurred early on, becoming less frequent as treatment progressed. As with other drugs of this class, a low incidence of myalgia, impotence and hair loss has been reported. Dizziness, drowsiness or tiredness have only rarely been reported in association with MODALIM. It is therefore unlikely to affect ability to drive or to use machinery. **NHS Price:** £13.72 per pack of 28 tablets. PL0071/0328. MODALIM is a trade mark. Further information is available on request from: Sanofi Winthrop Limited, One Onslow Street, Guildford, Surrey GU1 4YS. **References:** 1. Martin MJ *et al. Lancet* 1986; **2**: 933-936. 2. Pekkanen J *et al. N Engl J Med* 1990; **322** (24): 1700-1707. 3. European Atherosclerosis Society Study Group. *Eur Heart J* 1988; **9** (5): 571-600. 4. Farnier M *et al. J Drug Dev* 1992; **5** (1): 13-21.

LOWERS LDL

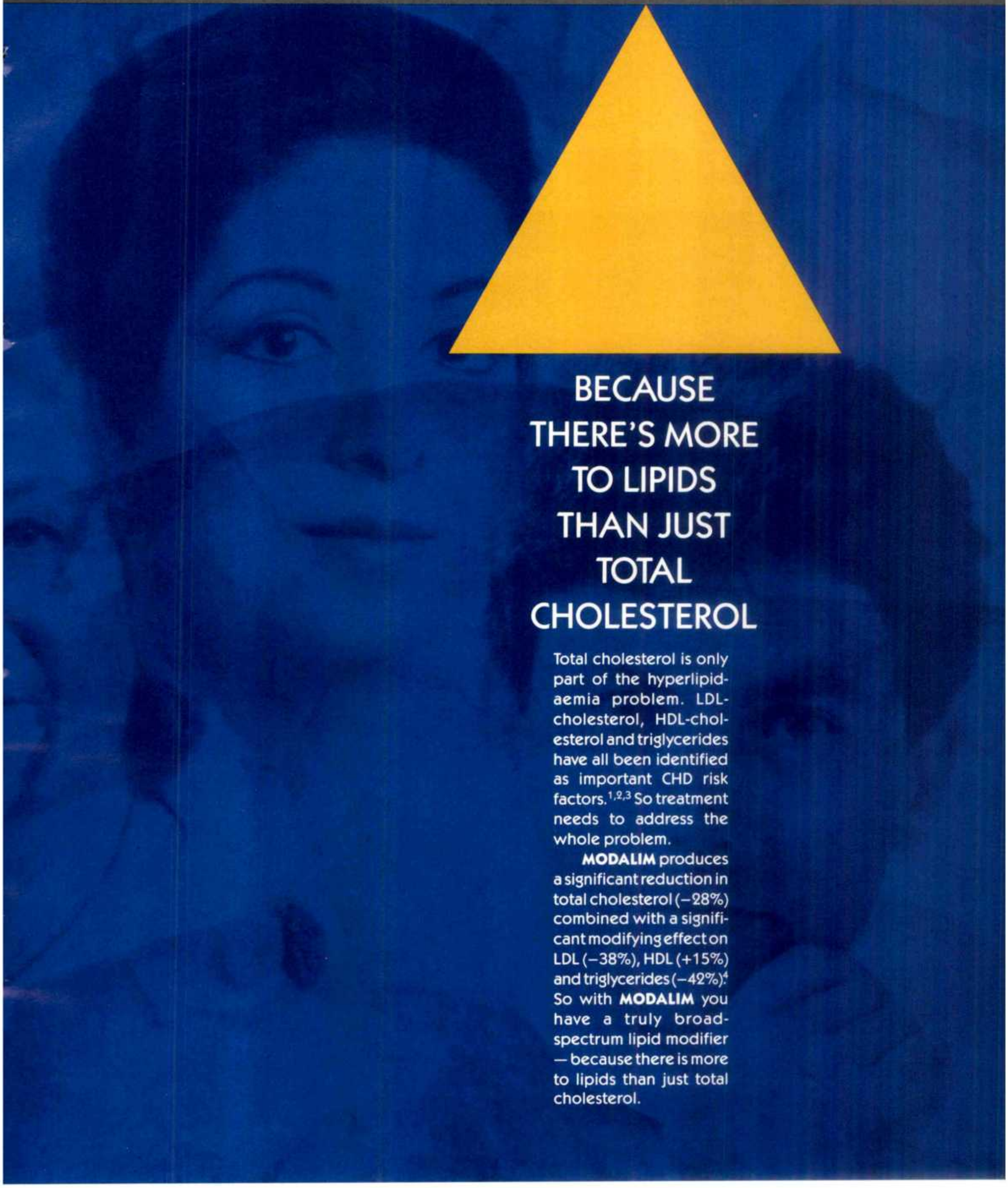
LOWERS



M O D

MODIFIES TH

RIGLYCERIDES RAISES HDL



BECAUSE THERE'S MORE TO LIPIDS THAN JUST TOTAL CHOLESTEROL

Total cholesterol is only part of the hyperlipidaemia problem. LDL-cholesterol, HDL-cholesterol and triglycerides have all been identified as important CHD risk factors.[1,2,3] So treatment needs to address the whole problem.

MODALIM produces a significant reduction in total cholesterol (−28%) combined with a significant modifying effect on LDL (−38%), HDL (+15%) and triglycerides (−42%).[4] So with **MODALIM** you have a truly broad-spectrum lipid modifier — because there is more to lipids than just total cholesterol.

ALIM

ciprofibrate

LIPID PROFILE

Having the time of their lives

Manoplax is an IP_3 (*inositol triphosphate*) attenuator, an entirely new class of agent for the treatment of heart failure which produces a balanced vasodilatory effect in both arterial and venous smooth muscle.[1]

Manoplax offers favourable haemodynamic effects which reduce breathlessness,[2] increase exercise capacity[1,2] as well as improving energy,[1] vitality[1] and sense of well-being.[1]

MANOPLAX™ ▼®
flosequinan

A new step forward in heart failure

Manoplax® ▼ Tablets

PRESENTATION Manoplax tablets are available as white, irregular hexagonal film-coated tablets containing either 50mg or 100mg of flosequinan. The tablets are debossed on one side with either '50' or '100' and debossed with an identifying motif on the other. **USES** Manoplax is indicated for the treatment of chronic congestive heart failure and should be used together with diuretics and, where appropriate, with a cardiac glycoside, with or without ACE inhibitors. **DOSAGE AND ADMINISTRATION** The recommended dose of Manoplax is 100mg per day taken as a single dose in the morning, with or without food. The starting dose should be 50mg once daily for four weeks after which the dose should be increased to 100mg. A minority of patients may benefit from a dose of 150mg once daily. As symptomatic benefits may take four to twelve weeks to become fully apparent, an increase to this dosage should not be considered for at least twelve weeks and only after a full assessment of the benefit to the patient. A maximum daily dose of 150mg should not be exceeded. At this dose, the heart rate should be monitored and the dose reduced if excessive increases are observed. In clinical trials, no problem specific to the elderly has been observed; nevertheless, as with all drugs, the frail elderly patient with a particularly low bodyweight may respond to a lower dosage. In patients with severe renal (creatinine clearance <20 ml/min) or hepatic impairment, the dose of Manoplax should be maintained at 50mg once daily. Manoplax is not recommended for use in children as the safety and efficacy of flosequinan in this group have not been established. **CONTRA-INDICATIONS, WARNINGS, ETC. Contra-indications:** History of hypersensitivity to Manoplax. Manoplax should not be used where the patient's heart failure is associated with outflow obstruction. **Pregnancy:** There is no evidence on the safety of the drug in human pregnancy. If drug therapy is needed in pregnancy, this drug should be used only if there is no safer alternative. It is not yet known whether flosequinan is excreted in human milk, therefore caution should be exercised if Manoplax is administered to nursing mothers. **Precautions:** Manoplax should be given with caution and under supervision to patients with a systolic blood pressure below 90mm Hg; therapy should be instituted with a dose of 50mg. As with all vasodilating drugs, symptomatic hypotension can occur, particularly following initial dosing, although this has only rarely been observed with Manoplax. Nevertheless, patients should be cautioned about its possible occurrence. The dose should be reduced if excessive increases in heart rate are observed. **Side effects:** Following treatment with Manoplax, the adverse events reported are mostly consistent with the vasodilatory actions of the drug, namely: headache, dizziness, palpitations, tachycardia and symptomatic hypotension. The headache usually resolves on continuation of therapy and medically significant, exaggerated first-dose hypotension has rarely been observed. Gastrointestinal effects include nausea, vomiting and diarrhoea. Taste disturbance, due to the secretion of the drug in the saliva, has also been reported. Minor serum creatinine elevation is seen in some patients but is not associated with a raised blood urea nitrogen. **Drug interactions:** In clinical studies, some patients receiving Manoplax required reduction of their warfarin dosage. A formal interaction study revealed only minor changes in coagulation parameters; nevertheless, it is advisable to monitor the coagulation status of patients receiving anticoagulants and Manoplax concurrently. There are no significant changes in the kinetics of either Manoplax or digoxin when they are administered concomitantly. Caution should be exercised in patients receiving vasodilators, although in patients receiving ACE inhibitors or nitrates, the addition of Manoplax has been well tolerated. Cimetidine alters the pharmacokinetics of flosequinan consistent with its known effect on the cytochrome P-450 enzyme system. This is considered to be of little clinical significance. **PHARMACEUTICAL PRECAUTIONS** None. **LEGAL CATEGORY** POM. **PACKAGE QUANTITIES** Manoplax Tablets 100mg: Blister calendar pack containing 28 tablets. Manoplax Tablets 50mg: Bottle pack containing 30 tablets. Basic NHS price Manoplax Tablets: calendar pack of 28 x 100mg - £42.56. Manoplax Tablets: bottle of 30 x 50mg - £41.10. **PRODUCT LICENCE NUMBERS** Manoplax Tablets 100mg: 0014/0428, Manoplax Tablets 50mg: 0014/0443. **DATE OF PREPARATION OR LAST REVIEW** 22 July 1992. Further information is available from Boots Pharmaceuticals, a division of The Boots Company PLC, Nottingham.

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Alcohol and sudden cardiac death

Goya Wannamethee, A G Shaper

Abstract

***Objective*—To assess the relation between alcohol intake and sudden cardiac death—ie, death within one hour of the onset of symptoms.**

***Design*—Prospective study of a cohort of men followed up for eight years.**

***Setting*—General practices in 24 towns in England, Wales, and Scotland.**

***Subjects*—7735 men aged 40–59 at screening who were selected at randon from one general practice in each of 24 towns.**

***Main outcome measure*—All deaths from ischaemic heart disease with particular reference to those that were sudden (death within one hour of the onset of symptoms).**

***Results*—During the follow up period of eight years there were 217 deaths from ischaemic heart disease of which 117 (54%) were classified as sudden. Although heavy drinkers (more than six drinks daily) did not show a high incidence rate of fatal heart attack, they showed the highest incidence rate of sudden cardiac death. This was seen in both manual and non-manual workers and was most clearly seen in older (50–59) men. Death from ischaemic heart disease was more likely to be sudden in heavy drinkers than in other drinking groups; this phenomenon was seen irrespective of the presence or degree of pre-existing ischaemic heart disease. The positive association between heavy drinking and the incidence of sudden death was most apparent in men without pre-existing ischaemic heart disease, with heavy drinkers showing an increase of >60% compared with occasional or light drinkers. After adjustment for age, social class, and smoking, heavy drinkers free of pre-existing ischaemic heart disease had a marginally significantly higher incidence rates of sudden death than other drinkers combined (relative risk 2·00, 95% confidence interval 0·98 to 4·8). Additional adjustment for systolic blood pressure reduced the risk to 1·7.**

***Conclusions*—This study suggests that heavy drinking is associated with an increased risk of sudden death. Studies that do not take pre-existing ischaemic heart disease into account are likely to underestimate the adverse effects of heavy drinking on the incidence of sudden death because the effects are not as evident in men with pre-existing ischaemic heart disease.**

(*Br Heart J* 1992;68:443–8)

There is evidence that heavy drinking can induce cardiac arrhythmias[1 2] and ventricular tachycardia,[3] which are both mechanisms associated with sudden death. However, there is no consistent evidence from population studies that heavy drinking is associated with an increased risk of sudden death.[4–9] Evidence for a strong association between alcohol and sudden death comes from studies on problem drinkers.[4 10–12] Although several prospective studies have shown death in heavy drinkers to be predominantly sudden,[8 9] the incidence of sudden death in these studies was not increased. Previous reports from the British Regional Heart Study have shown the prevalence of cardiovascular disease to be lowest in heavier drinkers possibly because of the tendency of men with ill health to drink less alcohol or abstain.[13 14] Most of the population studies relating alcohol to sudden death have not taken pre-existing ischaemic heart disease fully into account. This paper examines the role of alcohol in sudden death, looking at the *incidence* of sudden death during the follow up after initial screening, as well as at the *suddenness* of death in men with and without pre-existing ischaemic heart disease, to assess whether alcohol intake contributes to either the rate at which sudden death occurs or to the proportion of deaths that are sudden.

Subjects and methods

The British Regional Heart Study is a prospective study of cardiovascular disease in 7735 men aged 40–59 years selected from the age-sex registers of one group general practice in each of 24 towns in England, Wales, and Scotland. The criteria for selecting the town, the general practice, and the subjects as well as the methods of data collection have been reported.[15] Research nurses administered to each a standard questionnaire which included questions on smoking habits, alcohol intake, and medical history. Several physical measurements were made and blood samples (non-fasting) were taken for measurement of biochemical and haematological variables. The men were classified according to their current smoking status: those who had never smoked, ex-cigarette smokers, and current smokers. Those who had only ever smoked pipe/cigars were grouped as "never smoked". Ex-cigarette

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smokers who were currently pipe/cigar smokers were classified as ex-cigarette smokers. The longest-held occupation of each man was recorded and coded in accordance with the Registrar General's occupational classification.

ALCOHOL INTAKE

Alcohol consumption was recorded on the basis of questions on frequency, quantity, and type that were similar to those used in the 1978 General Household Survey. The men were classified into five groups according to their weekly alcohol intake: none, occasional (<1 unit/week), light (1–15 units/week), moderate (16–42 units/week), and heavy (>42 units/week—ie, more than six drinks daily). One unit of alcohol is defined as half a pint of beer, a single measure of spirits, or a glass of wine (approximately 8–10 g alcohol). Non-drinkers included both life-long abstainers and ex-drinkers. Twenty five biochemical and haematological measurements on a single blood sample taken when the questionnaire was completed indicated that the reported levels of alcohol consumption were valid on a group basis.[16]

Pre-existing ischaemic heart disease

The men were asked to recall a doctor diagnosis of angina or myocardial infarction and several other disorders listed on the questionnaire. The World Health Organisation (WHO) (Rose) chest pain questionnaire was administered to all men at the initial examination[17] and an electrocardiogram was recorded at rest from three orthogonal leads. The men were separated into three groups according to the evidence of ischaemic heart disease present at screening:

(I) No evidence of ischaemic heart disease on WHO chest pain questionnaire, electrocardiogram, or recall of a doctor diagnosis of ischaemic heart disease.

(II) Men with evidence suggesting ischaemic heart disease short of a definite myocardial infarction. This group contains those with electrocardiographic evidence of possible or definite mycardial ischaemia or possible myocardial infarction, those with angina or a possible myocardial infarction on WHO chest pain questionnaire, or with recall of a doctor diagnosis of angina.

(III) Men with a previous definite myocardial infarction on electrocardiogram or who recalled a doctor diagnosis of a heart attack. In the analyses men with pre-existing evidence of ischaemic heart disease consist of those in groups II and III.

FOLLOW UP

All men, whether or not they showed evidence of ischaemic heart disease at initial examination, were followed up for all cause mortality and cardiovascular morbidity.[18] Information on death was collected through the established "tagging" procedures provided by the National Health Service registers in Southport (England and Wales) and Edinburgh (Scotland). Mortality and major ischaemic heart disease events (fatal and non-fatal) are based on eight years of follow up for each man. Fatal events were defined as death from ischaemic heart disease (ICD 9th revision codes 410–414) as the underlying cause. *They comprised any death from ischaemic heart disease in an individual during the eight year follow up irrespective of a previous non-fatal event during that period.* The certifying doctor was asked to complete an enquiry form which asked the duration from onset of symptoms to death: less than one hour, 1–24 hours, or greater than 24 hours. Sudden cardiac death was defined as an event in which death occurred within one hour of the onset of symptoms. Only those for whom clear information was available regarding death within one hour were included as sudden deaths. Suddenness of death is defined as the proportion of the deaths from ischaemic heart disease in any group that were manifest as sudden. A non-fatal myocardial infarction was diagnosed according to WHO criteria.[19]

STATISTICAL METHODS

Multiple logistic regression was used to obtain rates and relative risks adjusted for the various risk factors. Alcohol was fitted as four dummy variables for the five alcohol categories (non, occasional, light, moderate, and heavy) and in some of the analyses as one dummy variable—ie, heavy versus the rest.

Results

During the follow up period of eight years there were 217 deaths from ischaemic heart disease of which 117 (53·9%) were classified as sudden, representing a crude attack rate for sudden cardiac death of 1·9/1000/year.

ALCOHOL AND SUDDEN DEATH FROM ISCHAEMIC HEART DISEASE

Figure 1 shows the crude attack rate/1000/year by alcohol intake for all deaths from ischaemic heart disease and for sudden and non-sudden deaths from ischaemic heart disease as well as the percentage of death manifest as sudden. Mortality from ischaemic heart disease decreased with increasing intake of alcohol intake up to levels of moderate drinking. Rates in heavy drinkers and light drinkers were similar. When deaths were separated into sud-

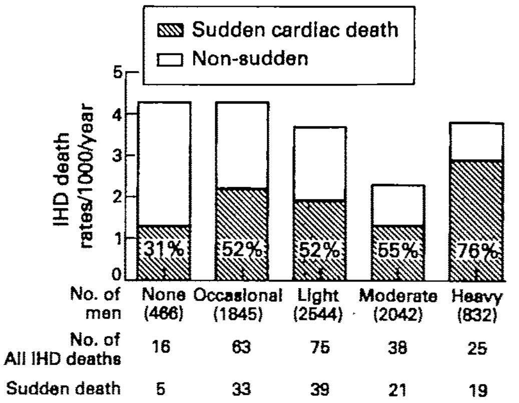
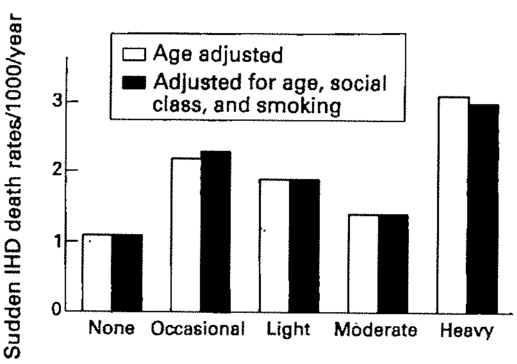


Figure 1 Alcohol intake and attack rate/1000/year for all deaths from ischaemic heart disease (IHD) sudden cardiac death and non-sudden death, and proportion (%) of IHD death manifest as sudden.

Figure 2 Alcohol intake and sudden death rates/1000/year adjusted for age and in addition for social class and smoking.



den and non-sudden deaths from ischaemic heart disease, there was a strong inverse association between alcohol intake and non-sudden death. For sudden death, however, there was no consistent pattern of relation except that heavy drinkers had the highest rates. Heavy drinkers had a significantly higher rate of sudden deaths than all other drinking groups combined (relative risk (RR) = 1·6, 95% confidence interval (CI) 1·0 to 2·6, p = 0·05). Although heavy drinkers did not have an excess risk of overall death from ischaemic heart disease, death in heavy drinkers was more likely to be sudden than in any other drinking category. Seventy six percent of deaths from ischaemic heart disease in heavy drinkers occurred suddenly compared with 31% in non-drinkers. Among occasional, light, and moderate drinkers the proportion of suddenness of death was similar. Adjustment for age made little change to the overall relation between alcohol intake and risk of sudden death: heavy drinkers still showed the highest risk (fig 2). Indeed, since heavy drinkers tend to be younger, their relative risk increased with adjustment for age compared with all other drinking groups combined (RR = 1·8, 95% CI 1·1 to 2·9). Since alcohol has been shown in this study to be strongly associated with smoking and social class, further adjustments were made for social class and smoking. This also made little difference to the relation already observed (fig 2): heavy drinkers showed significantly higher risk than all other drinkers combined (RR = 1·73, 95% CI 1·06 to 2·86, p = 0·03).

ALCOHOL, AGE, AND SUDDEN DEATH

We examined the relation between alcohol intake and sudden death in two age groups (table 1). Only in the older age group (50–59) was heavy drinking clearly associated with an increased risk of sudden death. In the younger age group occasional and heavy drinkers had similar rates, which were higher than those seen in other categories.

Table 1 Alcohol intake and sudden death rates/1000/year by age

	Age-group			
	40–49		*50–59*	
Alcohol intake	*No.*	*Rate*	*No.*	*Rate*
None	0	0	5	2·1
Occasional	11	1·5	22	2·9
Light	8	0·9	31	2·9
Moderate	1	0·1	20	2·5
Heavy	5	1·4	14	4·5
Total	25		92	

ALCOHOL, SMOKING, AND SUDDEN DEATH

Since alcohol intake is strongly associated with smoking status we have examined the relation between alcohol and sudden death according to smoking (data not presented). Only 14 of the 117 sudden deaths occurred in men who had never smoked so that no inference can be drawn about the alcohol-sudden death relation in this group of men. In ex-smokers (38 deaths), although the incidence of sudden death in heavy drinkers was not higher than in lighter drinkers, deaths in heavy drinkers were more likely to be sudden (75%) compared with the other drinking categories (50%). In current smokers (65 deaths), heavy drinkers had the highest absolute risk of sudden death, and death was also more likely to be sudden (75%).

ALCOHOL, SOCIAL CLASS, AND SUDDEN DEATH

We examined the relation between alcohol intake and sudden death separately in manual and non-manual workers. The incidence of sudden death was highest in heavy drinkers in both social classes even after adjusting for age and smoking but was most pronounced in manual workers. The adjusted relative risk of sudden death in heavy drinkers compared with all other drinking groups was 1·44 (99% CI 0·49 to 4·30) and 1·60 (95% CI 0·88 to 2·93) in non-manual and manual workers respectively. In both social classes deaths from ischaemic heart disease in heavy drinkers were also more likely to be sudden (100% in non-manual and 68% in manual workers).

PRE-EXISTING ISCHAEMIC HEART DISEASE, ALCOHOL, AND SUDDEN DEATH

We examined the relation between alcohol and sudden death separately in men with and without pre-existing ischaemic heart disease. Table 2 shows the crude mortality rates for all deaths from ischaemic heart disease and for sudden and non-sudden deaths from ischaemic heart disease according to the evidence of pre-existing ischaemic heart disease. Table 2 also shows age adjusted sudden death rates in the two groups.

Men with no evidence of ischaemic heart disease—No association was seen between alcohol intake and all deaths from ischaemic heart disease. Non-drinkers had the lowest rates of death from ischaemic heart disease. However, the risk of sudden death was significantly increased in heavy drinkers (p < 0·05), who showed more than a twofold increase in risk compared with all other drinking groups after we adjusted for age (RR = 2·3, 95% CI 1·1 to 4·7). Indeed 82% of deaths occurring in heavy drinkers were manifest as sudden. There was a strong inverse relation between alcohol intake and non-sudden death.

Men with pre-existing ischaemic heart disease—In those with evidence of pre-existing ischaemic heart disease, non-drinkers showed the highest rate of deaths from ischaemic heart disease and moderate drinkers had the lowest rate. Heavy drinkers had rates lower than

Table 2 Alcohol intake and crude rate/1000/year for all deaths from ischaemic heart disease (IHD) sudden and non-sudden IHD death and proportion of IHD deaths manifest as sudden in men with and without pre-existing IHD

Alcohol intake	*No of men*	*All IHD deaths rate/1000*	*Sudden*	*Non-sudden*	*Percentage sudden*	*Age adjusted sudden death rate 1000 yr*
			No evidence of IHD			
None	320	1·2 (3)	0	1·2 (3)	0	0
Occasional	1379	2·5 (26)	1·1 (12)	1·4 (14)	46·2%	1·1
Light	1953	2·1 (33)	1·0 (15)	1·1 (18)	45·5%	0·9
Moderate	1534	1·5 (18)	0·8 (10)	0·7 (8)	55·6%	0·8
Heavy	602	2·3 (11)	1·9 (9)	0·4 (2)	81·8%	2·0
Total	5788	2·0 (91)	1·0 (46)	1·0 (45)	50·5%	
			Evidence of IHD			
None	146	11·1 (13)	4·3 (5)	6·8 (8)	38·5%	4·0
Occasional	466	9·9 (37)	5·6 (21)	4·3 (16)	56·8%	5·6
Light	591	8·9 (42)	5·1 (24)	3·8 (18)	57·1%	4·9
Moderate	508	4·9 (20)	2·7 (11)	2·2 (9)	55·0%	2·8
Heavy	230	7·6 (14)	5·4 (10)	2·2 (4)	71·4%	5·8
Total	1941	8·1 (126)	4·6 (71)	3·5 (55)	56·3%	

Numbers in parentheses are deaths.

occasional and light drinkers. The overall pattern was somewhat U-shaped. No association was seen between alcohol intake and the incidence of sudden deaths, but deaths from ischaemic heart disease in heavy drinkers were far more likely to be sudden (71% *v* 38% in non-drinkers). A strong inverse association was seen for non-sudden death. Although the incidence of sudden death was significantly increased in men with pre-existing heart disease (4·6/1000/year *v* 1·0/1000/year in men free of ischaemic heart disease), the proportion of death manifest as sudden was similar in both groups (50·5% *v* 56·3%).

ALCOHOL AND SUDDEN DEATH IN MEN WITH NO EVIDENCE OF ISCHAEMIC HEART DISEASE

Table 3 shows the relative risk of sudden death by the five alcohol categories adjusted for age and in addition for social class and smoking in men with no evidence of ischaemic heart disease. After adjustment for age, heavy drinkers had a significantly increased risk of sudden death compared with all drinking categories combined ($p < 0·05$). Although the numbers are small, after adjustment for age, social class, and cigarette smoking heavy drinkers had a twofold increase in risk of sudden death compared with all other drinkers combined. This difference was of marginal significance ($p = 0·06$). It is well established that heavy drinking raises blood pressure. To assess the effect of blood pressure on the relation between alcohol and sudden death we further adjusted for systolic blood pressure (table 3). This reduced the higher rates in heavy drinkers substantially. Compared with all the other drinking groups the risk was reduced from 2·03 to 1·73 and was no longer significant ($p = 0·15$). To assess whether the increased risk of sudden death in heavy drinkers could be attributed to antihypertensive treatment we examined the relations in table 3 after we excluded all men on regular antihypertensive treatment. Heavy drinking was still associated with a more than twofold increase in risk (RR = 2·25). Further adjustment for sysolic blood pressure reduced the risk to 1·88, a similar level of risk seen when all men were included. This suggests that the increased incidence of sudden death in heavy drinkers is partly attributed to systolic blood pressure but not to antihypertensive therapy.

HEART RATE

Raised systolic blood pressure is associated with increased heart rate ($r = 0·2$, $p < 0·0001$). Adjustment for heart rate in addition to age, smoking, and social class resulted in a small reduction in relative risk (RR = 1·97). Additional adjustment for systolic blood pressure further decreased the relative risk to 1·67, indicating that heart rate alone was not responsible for the increased risk.

Discussion

In this study of middle aged British men we found a positive association between heavy drinking (>6 drinks daily) and the risk of sudden death: with heavy drinkers showing nearly a twofold increase in risk compared with other drinking categories combined. The increased incidence of sudden death in heavy drinkers was more pronounced in the older age group (50–59) and was seen in both social classes. The positive association was most clearly seen in those with no evidence of pre-existing ischaemic heart disease even after adjustment for age, social class, and smoking. Fatal heart attacks in heavy drinkers were predominantly sudden irrespective of age, social class, cigarette smoking, and presence of pre-existing ischaemic heart disease. Heavy drinking raises blood pressure, and about 10%

Table 3 Alcohol intake and adjusted relative risk (95% CI) of sudden death in men with no evidence of IHD

	Age	*Age + smoking + social class*	*Age + smoking + social class + SBP*
None	0	0	0
Occasional	1·00	1·00	1·00
Light	0·86 (0·40, 1·84)	0·86 (0·38, 1·82)	0·86 (0·38, 1·90)
Moderate	0·76 (0·32, 1·80)	0·76 (0·30, 1·70)	0·71 (0·26, 1·67)
Heavy	1·88 (0·78, 4·48)	1·65 (0·68, 4·1)	1·37 (0·30, 3·30)
Heavy vs rest	2·30 (1·11, 4·73)	2·03 (0·98, 4·28)	1·73 (0·81, 3·68)

SBP, systolic blood pressure.

of hypertension in middle-aged men may be attributed to heavy drinking.[20] The increased incidence of sudden death in heavy drinkers in this study is partly attributed to the rise in systolic blood pressure associated with heavy drinking. After adjustment for systolic blood pressure there was still an increased incidence of sudden death (RR = 1·73) though the difference between heavy drinkers and other categories combined was not significant, possibly because of small numbers. These results and the finding that deaths from ischaemic heart disease in heavy drinkers are predominantly sudden suggest that alcohol may have a direct effect on initiating sudden cardiac death.

PRE-EXISTING ISCHAEMIC HEART DISEASE

About 50% of those who die suddenly have symptoms or evidence of ischaemic heart disease before the event.[21,22] People who develop ischaemic heart disease have an increased tendency to reduce or stop alcohol intake,[13,14] so that studies that do not take pre-existing ischaemic heart disease into account are likely to underestimate the effects of heavy drinking on the incidence of sudden cardiac death. When we examined the relation between alcohol and incidence of ischaemic heart disease death in all men (including those with pre-existing ischaemic heart disease), heavy drinkers did not show excess risk of deaths from ischaemic heart disease but they showed the highest incidence rates of sudden cardiac death (fig 1). The increased risk was most apparent in men without evidence of ischaemic heart disease, with heavy drinkers showing a significantly increased risk of sudden death (table 2). In those with pre-existing evidence of ischaemic heart disease, the incidence of sudden death was not increased in heavy drinkers. This group contains men with a wide range of severity and it is likely that even in this group those who remain heavy drinkers may have less severe ischaemic heart disease and thus be at lower risk of having a fatal attack. When we examined the relation separately in the small group of men with definite myocardial infarction (428 men), heavy drinking was associated with an increased but non-significant incidence of sudden cardiac death. However, in men both with and without pre-existing ischaemic heart disease the proportion of deaths that were sudden was highest in the heavy drinkers.

RETROSPECTIVE STUDIES

A study of 100 people who died suddenly and had a coroner's necropsy in Newcastle-upon-Tyne showed a higher proportion of men had taken alcohol three hours before death than those who had a non-fatal myocardial infarction.[23] Sudden death was defined as occurring less than 24 hours after onset of symptoms but 73% took place within one hour. Interestingly, sudden death was most common on Saturdays, when drinking is most frequent and this was not seen for non-fatal myocardial infarction. Further, the sudden death group contained twice the proportion of men from social classes IV and V than the non-fatal myocardial infarction group (45% *v* 22%). In the British Regional Heart Study we did not observe any difference in the occurrence of sudden death from ischaemic heart disease by day of the week but the effect of heavy drinking on the incidence of sudden death was more pronounced in manual workers than in non-manual workers. In the Auckland Study, which used community-based registers for myocardial infarction, heavy drinking discriminated between sudden (<24 hours) and non-sudden death.[7]

HEAVY DRINKING IN THE GENERAL POPULATION

Although large population studies have shown problem drinking to be associated with a significant increase in risk of sudden death,[4,11,12] the association between heavy drinking (variously defined) in the general population and sudden cardiac death has been inconsistent. Although most population studies have reported an inverse or U-shaped relation between alcohol intake and coronary heart disease mortality,[24] studies which have examined the relation between alcohol intake and sudden cardiac death as a separate end point found a positive association or no association between heavy drinking (variously defined) and sudden death. In most of these studies, pre-existing ischaemic heart disease was not taken into account and in the ones that did so only men with definite ischaemic heart disease (variously defined) were excluded. In a prospective study of Finnish men aged 40–64 followed for five years, the sudden death reate increased with increasing alcohol intake and was more pronounced in the older men (over 50 years).[6] This is consistent with the present study which found the incidence of sudden death to be much higher in heavy drinkers in the older age group (table 2). In the younger age groups (40–49 years) the incidence rate in heavy drinkers was similar to that in occasional drinkers. The increased rate of sudden death in younger occasional drinkers suggests that some of these may be binge drinkers, a condition that has been shown to be associated with cardiac arrhythmias which may lead to sudden death.[2] In the Framingham study though the incidence of sudden death increased with age, deaths from ischaemic heart disease in younger men were more likely to be sudden.[21] It is possible that occasional binge drinking in younger men may be responsible for this finding.

In a five year follow up of 269 755 American men aged 20–65 employed in the telephone industry, heavy drinking (>5 drinks a day) was associated with an increased risk of arrhythmic death but not with death in circulatory failure.[25,26] However, in multivariate analysis, which included smoking and blood pressure among other variables, alcohol did not remain a significant predictor.[26]

In the Framingham study, heavy drinking was apparently associated with unexpected sudden death—that is, sudden death in the absence of prior evidence of ischaemic heart disease.[5] In both the Puerto Rican study[8] and the Yugoslavian study[9] no association was found between alcohol intake and the *incidence* of sudden death. However, in both these studies deaths from ischaemic heart disease in heavy drinkers were predominantly sudden (100% and 85% respectively). In the British Regional Heart Study the positive association between heavy drinking and sudden death was less pronounced when pre-existing ischaemic heart disease was not taken into account. In the Puerto Rican study pre-existing ischaemic heart disease was not taken into account. In the Yugoslavian study only men with definite coronary heart disease were excluded. The positive association between heavy drinking and the incidence of sudden death is therefore likely to be underestimated in both these studies.

NON-SUDDEN DEATH

A strong inverse association that was apparent at levels of moderate drinking or above was observed with non-sudden death in this study even in men without pre-existing ischaemic heart disease. In men with pre-existing ischaemic heart disease the inverse relationship appeared to be continuous from non-drinkers through to heavy drinking. These findings suggest that alcohol may play a protective role in non-sudden fatal ischaemic heart disease but at levels of drinking which are associated with increased all-cause mortality and with several aspects of morbidity.[27]

SUDDENESS OF DEATH

In most studies the conventional risk factors for ischaemic heart disease—smoking, blood cholesterol, and systolic blood pressure—have all been shown to be strongly predictive of the *incidence* of sudden death.[22, 28-31] However, these predictors have not been found to distinguish between the modes of death.[22, 31] The risk profile of an individual who dies suddenly cannot be distinguished from that of an individual who succumbs more slowly to ischaemic heart disease. However, findings from the British Regional Heart Study, the Auckland Study,[7] the Puerto Rican study,[8] and the Yugoslavian study[9] indicate that death in an event of a heart attack in heavy drinkers was most likely to be sudden and that heavy drinking helps to discriminate between sudden death and non-sudden death.

In middle aged men in the British Regional Heart Study with no pre-existing ischaemic heart disease there was evidence that heavy drinking was associated with an increase in the *incidence* of sudden death as well as with the *suddeness* of death. Although the overall death rate from ischaemic heart disease was not high compared with lighter drinkers, the increased incidence rate of sudden deaths in heavy drinkers and the findings that deaths from ischaemic heart disease in heavy drinkers are predominantly sudden suggests that heavy drinking may precipitate arrhythmia and sudden cardiac arrest. The mechanism by which systolic blood pressure is associated with sudden cardiac death is uncertain. Several other studies also indicate that heavy drinking helps to discriminate between sudden death and non-sudden death. There is evidence from this study that heavy alcohol consumption may be a causative factor in sudden cardiac death. This has important implications in the aetiology and prevention of sudden death in all subjects but particularly those without pre-existing ischaemic heart disease.

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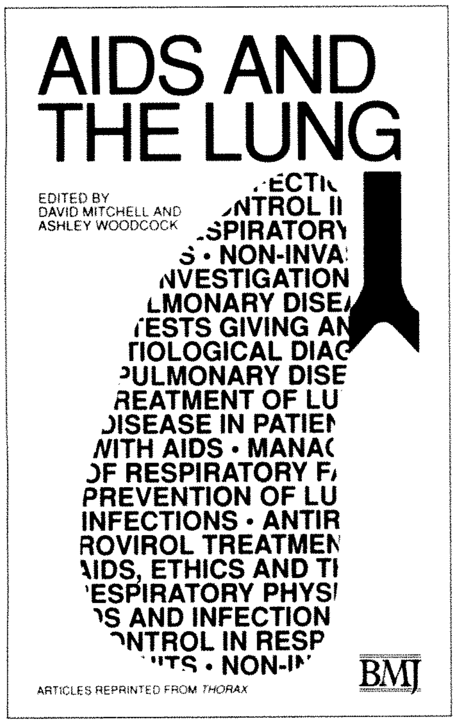
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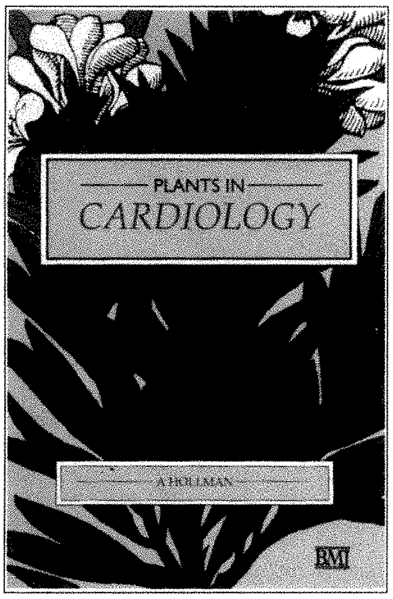

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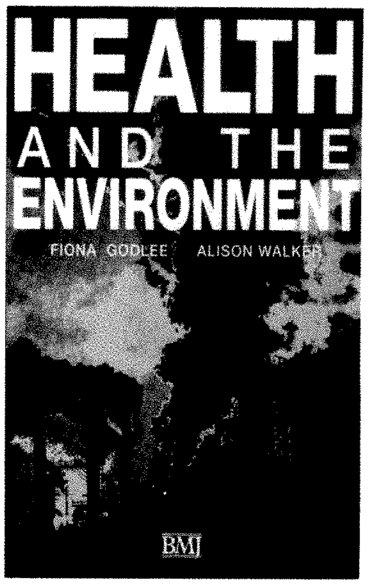

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Br Heart J 1992;68:449–53

Streptokinase resistance: when might streptokinase administration be ineffective?

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Abstract

Objective—(_a_) To develop an assay for streptokinase resistance. (_b_) To determine the prevalence of streptokinase resistance in patients presenting with acute myocardial infarction for the first time. (_c_) To determine the prevalence of streptokinase resistance in patients after exposure to streptokinase or streptococcal infection.

Design—Open, prospective.

Patients—30 healthy volunteers. 40 patients admitted to the coronary care unit at Addenbrooke's Hospital with suspected acute myocardial infarction, 12 patients 12 months after streptokinase treatment, eight patients 24 months after streptokinase treatment, and sera from 12 patients with raised antistreptolysin O (ASO) titres.

Methods—Three assays were used; a dilution neutralisation assay, an enzyme linked immunosorbent assay (ELISA) for immunoglobulin G (IgG) antistreptokinase antibodies, and an in vitro fibrin plate lysis assay. All measurements were performed on venous blood samples.

Results—Neutralisation and IgG antibody titres were positively correlated. Mean (SEM) antistreptokinase concentrations in the 30 controls were 87 (10) U/ml (neutralisation assay) and 28 (6·3) U/ml (ELISA). Corresponding concentrations in patients before streptokinase were 68 (6·1) U/ml and 18 (4·5) U/ml with a mean fibrin plate assay 117 (7·1)% that of controls. Resistance to streptokinase was detectable in one patient after 72 hours and in all patients by day 10. By day 10 concentrations were 4388 (919) U/ml, 773 (109) U/ml, and 17 (5·4)%. At both 12 and 24 months resistance was present in 75% of patients. Similarly 66% of high ASO titre sera showed resistance. The fibrin plate lysis assay detected significantly reduced streptokinase dependent fibrinolysis in vitro in the absence of raised total concentrations of antistreptokinase antibodies.

Conclusions—The prevalence of streptokinase resistance in patients presenting with their first myocardial infarction is low. Resistance develops early after treatment and is still present in 75% of patients after 24 months. Retreatment with streptokinase is likely to be suboptimal even after 24 months. The fibrin plate lysis assay detects resistance in patients with normal concentrations of streptokinase antibodies. Streptococcal infection is associated with a high incidence of streptokinase resistance.

(_Br Heart J_ 1992;68:449–53)

Thrombolysis has become an essential component of the management of an acute myocardial infarction. Large controlled trials have shown that streptokinase compares favourably with other fibrinolytic agents in terms of efficacy, side effects, and cost.[1–5] It is therefore likely to remain the thrombolytic agent of choice in the United Kingdom for the foreseeable future. Because of its antigenic nature, however, the presence of neutralising antibodies in some patients may reduce its effectiveness. Rapid development of immunoglobulin G (IgG) antibodies to streptokinase has been reported,[6] and antibodies have been detected up to eight months after treatment.[7] Current recommendations advise against retreatment with streptokinase within six months and immediately after a streptococcal infection.[8 9] The prevalence of antistreptokinase antibodies in the general population and in patients presenting to the coronary care unit for the first time is unknown, and their potential to neutralise a standard dose of streptokinase has not been rigorously evaluated.

To test whether the development of antibodies is associated with significant streptokinase resistance we have developed an in vitro fibrin plate lysis assay and correlated this with both functional and immunological concentrations of streptokinase antibodies. A normal range for neutralising activity was established in a group of normal subjects. Patients admitted to a coronary care unit with suspected myocardial infarction were investigated on arrival and, to determine how soon and for how long neutralising activity was present, blood samples were taken early (three to ten days) and late (12 and 24 months) after streptokinase treatment. We also tested sera from patients with raised antistreptolysin O (ASO) titres for streptokinase neutralising activity to confirm whether recent streptococcal infection precluded administration of streptokinase.

Patients and methods

PATIENTS AND CONTROLS

Over a six week period, venous blood samples were taken before administration of streptokinase, from 40 patients admitted to the coronary care unit of Addenbrooke's Hospital for the first time with a suspected acute myocardial infarction. Further samples were taken on days three to four and on the day of discharge (days seven to 10) from 15 patients who had received 1·5 million units of intravenous streptokinase (Streptase, Hoechst). None of the patients had previously received streptokinase. Venous blood was also taken from (*a*) 12 patients who had received streptokinase 12 months previously, (*b*) eight patients who had received streptokinase 24 months previously, (*c*) 12 patients with raised antistreptolysin O titres, (*d*) 30 healthy normal controls with no documented history of streptococcal infection. All patients gave informed verbal consent, and the study was approved by the local ethics committee.

MEASUREMENT OF STREPTOCOCCAL ANTIBODIES

Immunoglobulin G antibodies to streptokinase were measured by an enzyme linked immunosorbent assay (ELISA) incorporating solid phase streptokinase. Neutralising antibodies were measured by a dilutional clot lysis assay.

(*a*) ELISA assay: 100 μl of 1000 U/ml streptokinase (Streptase, Hoechst) was added to the wells of a microtitre plate (Nunc, Denmark). Plates were sealed, incubated overnight at room temperature, and washed three times in 0·01 mol/l phosphate buffered saline (PBS) and 0·5 ml/l Tween. One hundred μl of plasma, diluted one in 40 with phosphate buffered saline (PBS)/0·1% bovine serum albumin, was then added to each well and incubated for two hours at room temperature. After three washes the wells were incubated with 100 μl peroxidase-conjugated rabbit antihuman IgG (Dako) diluted 1/5000 in PBS/Tween for two hours at room temperature. After washing, 100 μl substrate solution (3 mg/ml orthophenylenediamine in 0·01 mol/l citrate phosphate buffer, with 0·01% hydrogen peroxide was added and the reaction stopped by the addition of 150 μl sulphuric acid. Absorbance at 492 nm was read with a Titertek Multiscan plate reader. A standard curve was derived from doubling dilutions of normal plasma from 1/20, assigned 100 U/ml and patient samples were sufficiently diluted to enable a concentration of antibody to be found from the standard curve. The concentration of antibody in the patient sample was then multiplied by the appropriate dilution factor. A concentration >2 SDs above the mean of the normal controls was defined as raised.

(*b*) Neutralisation assay: streptokinase neutralising activity was measured by a method similar to that previously reported.[7] Streptokinase was diluted in saline to give a range of concentrations from 500 U/ml to 2000 U/ml. Twenty μl of each dilution was added to 200 μl plasma and a fibrin clot formed by the addition of 1 U bovine thrombin (Diagen). The highest concentration of streptokinase that failed to lyse the clot was used to calculate the streptokinase neutralising titre. Patient samples were diluted in normal plasma until clot lysis was achieved. The neutralising activity (U/ml) was calculated as:— highest concentration of streptokinase failing to lyse clot × dilution of test plasma in normal plasma/10. A concentration >2 SDs above the mean of the normal controls was defined as raised.

FIBRIN PLATE LYSIS ASSAY

Fibrinogen (Diagen) was dissolved in imidazole buffer to a concentration of 650 mg/l. Fibrin plates were prepared by clotting 10 ml fibrinogen solution with 10 U bovine thrombin (Diagen) and 25 mM calcium chloride in petri dishes (Sterilin). Streptokinase was added to the plasma samples to achieve a concentration of 625 U/ml. This was the calculated plasma concentrations of streptokinase that would result from a dose of 1·5 million units to a 70 kg subject with a packed cell volume of 45%. Twenty five μl of each plasma sample were placed on a fibrin plate and incubated at 37°C for 24 hours. The area of lysis was calculated as the product of two diameters at 90° to each other. The mean area of lysis of the 30 normal controls was 1394 mm^2. All areas of lysis caused by patients plasma with added streptokinase were then reported as percentages of this value. A reduction in streptokinase dependent in vitro fibrinolysis >2 SDs below the mean normal activity was regarded as abnormal.

ASO TITRES

Titres of ASO were measured by a standard sheep red cell haemolysin assay (Wellcome Diagnostics).

STATISTICAL ANALYSIS

Comparisons between study groups and the normal controls were performed with the Wilcoxon's ranking test for unpaired data (Mann-Whitney test). The same test was used for comparisons in the group tested on several days as the numbers tested on each day varied.

Results

The mean age of the 40 patients (28 men) admitted to the coronary care unit was 58 (range 38–71) years. All patients received 1·5 million units of streptokinase by a one hour intravenous infusion. None of the patients suffered an allergic reaction. Venous blood samples were taken from 15 patients on day 3 and on the day of discharge (days 7/8 in seven patients and days 9/10 in eight patients).

The ELISA assay and the neutralisation titre assay produced comparable results and were positively correlated ($r = 0·55$; $p < 0·001$). Overall neither assay was correlated with the fibrin plate lysis assay. Between days 1 and 10 after streptokinase, however, a reduction (more than 2 SD below mean normal) in fibrin plate lysis was associated with antistreptokinase IgG concentrations above 155 U/ml and a neutralisation titre above 375 U/ml. The table shows the normal ranges and the concentrations found in each patient group for each assay.

Mean (SEM) in each study group for each assay

Method	*Normal controls (n = 30)*	*Admitted patients (n = 40)*	*Serial values in treated patients (n = 15)*				*Patients at 12 months (n = 12)*	*Patients at 24 months (n = 8)*	*High ASO titre sera (n = 12)*
			Day 0 (n = 15)	*Day 3/4 (n = 15)*	*Day 7/8 (n = 7)*	*Day 9/10 (n = 8)*			
Neutralising titre (U/ml)	87 (10·0)	—	68 (6·1)	375*** (127)	2053*** (818)	4388*** (919)	150*** (32·3)	—	—
ELISA IgG antistreptokinase (U/ml)	28 (6·3)	17 (3·4)	18 (4·5)	38 (30·7)	311*** (133)	773*** (109)	120*** (24·9)	140** (27 6)	177** (44 3)
Fibrin plate lysis assay as % of mean normal	100% (4·0%)	—	117% (7·1%)	108% (14·1%)	34%*** (15·6%)	17%*** (5·4%)	43%*** (9·7%)	40%** (9·1%)	50%** (10·1%)

**p < 0 01; ***p < 0·001.

Fibrin plate lysis in the 30 normal controls (mean age 49, range 34–64 years, 10 women) in the absence of streptokinase was less than 2% of that in the presence of streptokinase.

None of the patients admitted to the coronary care unit had raised concentrations of IgG antistreptokinase antibodies on admission. In 15 of these patients neutralisation titres and fibrin plate lysis values were also measured. None had evidence of either neutralising antibodies or impaired in vitro fibrinolytic responses to streptokinase.

By days 3/4 (n = 15) the neutralising titre had risen above the normal range (>2 SDs above the mean) in nine patients (range 200 to 2000 U/ml). Eight of these, however, showed no increase in antistreptokinase IgG by ELISA and no reduction in fibrinolytic activity in the fibrin plate lysis assay. One patient had a rise in neutralising titre to 2000 U/ml and an ELISA IgG of 437 U/ml. This was associated with a reduction of in vitro fibrinolysis to 6% of control values.

By days 7/8 (n = 7) the neutralisation titre was above the normal range in all patients and IgG antibodies were above normal in all but two. Only the patients with raised IgG antibodies had significantly reduced fibrinolytic responses. By day 10 (n = 8) all patients had raised antibody concentrations by both assays with reduced fibrinolytic responses to a mean value of 17% (range 1% to 54%) of controls. The day 7–10 results were significantly different from the normal control and day 0 results for each of the three assays (p < 0·001). Figures 1 and 2 show the IgG antistreptokinase concentrations and the fibrinolytic responses over the 10 day study period.

Of the 12 patients studied 12 months after being given streptokinase (mean age 56, range 36–70 years, two women), only three had a raised neutralisation titre, but six had raised IgG concentrations. All six of these had reduced fibrin plate lysis values (range 10%–35%). An additional three patients, however, with IgG concentrations within the normal range also had impaired fibrinolysis (10%, 32%, 38%). Only three patients had no evidence of streptokinase resistance by any method.

Of the eight patients studied at 24 months (mean age 53, range 43–62 years, two women), six had reduced fibrin plate lysis (range 3%–24%). Five of these six had raised IgG concentrations.

Of the 12 sera from patients with raised ASO titres, six had raised ELISA IgG concentrations and all of these, plus two with concentrations within the normal range, had reduced fibrin plate lysis values (range 9%–64%). Figure 3 shows the individual and mean fibrinolytic responses of each of the study groups.

Discussion

None of the patients admitted with acute myocardial infarction had raised concentrations of antistreptokinase antibodies or in vitro fibrinolytic resistance to streptokinase. The prevalence of antistreptokinase antibodies in patients presenting to the coronary care unit for the first time is therefore low and most should

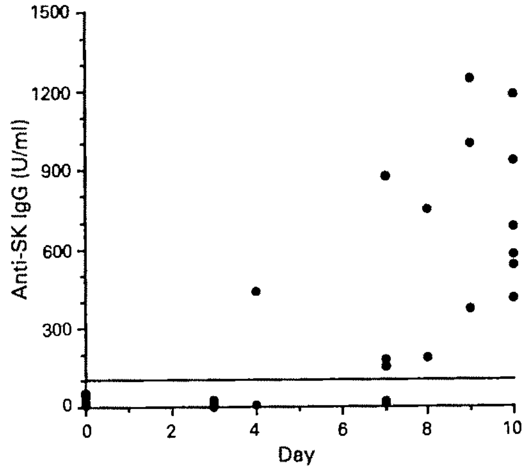

Figure 1 Antistreptokinase (Anti-Sk) IgG antibody concentrations measured by ELISA over the 10 day period after 1·5 million units of intravenous streptokinase in 15 patients (all patients were tested on day 0, days 3/4 and days 7/10 and many points overlap). Horizontal line indicates mean (+2 SDs) for normal control group.

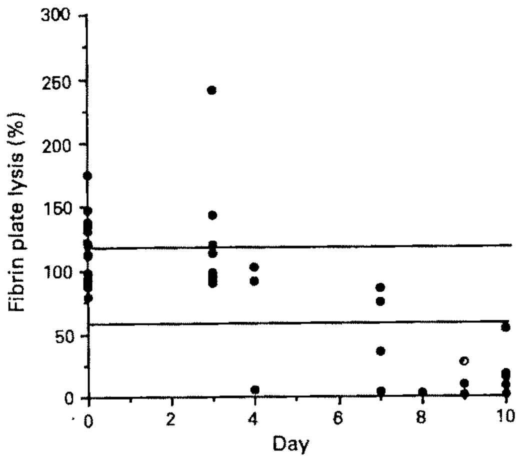

Figure 2 Fibrin plate lysis (%) relative to mean normal result over the 10 days after 1·5 million units of intravenous streptokinase in 15 patients (all patients were tested on day 0, days 3/4 and days 7/10 and many points overlap). Horizontal lines indicate mean (2 SDs) for normal control group.

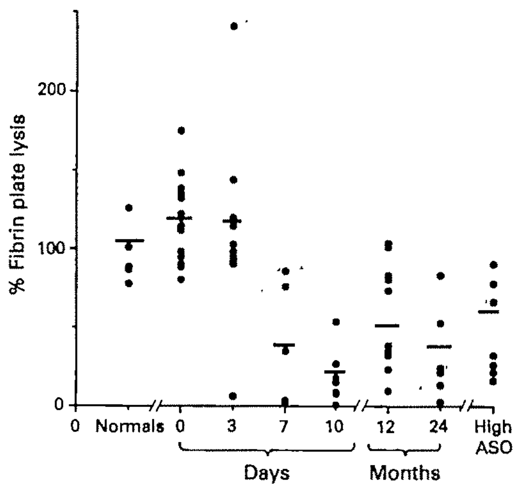

Figure 3 Individual values (point) and mean values (bar) of fibrin plate lysis in each of the study groups. Values for many patients overlap.

respond to a standard dose of streptokinase. This is despite the fact that many of them will have encountered streptococci in the past.

By days three to four there had been a slight increase in neutralising antibody concentrations; however, in only one patient was this substantial enough to cause a reduction in streptokinase induced fibrinolysis. Thus retreatment with streptokinase within 72 hours of the initial dose is likely to be successful in most patients but may result in impaired thrombolysis in some. By day seven most patients had streptokinase resistance and by day 10 all patients had resistance. This time course suggests a primary rather than secondary antibody response to streptokinase.

Patients studied 12 months after a dose of streptokinase had varying concentrations of antibodies. Nevertheless, nine (75%) of them still had significantly impaired fibrin plate lysis. Of the eight patients studied at 24 months six (75%) still had impaired fibrin plate lysis. Therefore, roughly three quarters of patients might be expected to have some degree of resistance to streptokinase, even after 12 or 24 months. Further information on the effects of streptokinase resistance on drug readministration is urgently required. Similarly, roughly two thirds of patients with serological evidence of recent streptococcal infection are likely to have impaired thrombolysis with streptokinase (eight of 12 patients). The precise temporal relation between streptococcal infection and streptokinase resistance also warrants further study.

A reduction of in vitro fibrinolysis might reasonably be expected to predict a decrease in thrombolytic activity in vivo. However, it was not possible in this study to determine to what extent the two are correlated. In the 10 days after a dose of streptokinase raised concentrations of antistreptokinase antibody measured by the neutralisation assay were not necessarily associated with reduced in vitro fibrinolysis. By contrast, a raised ELISA IgG titre was always associated with reduced fibrinolysis. In these patients an increase in IgG antibodies is likely to predict impaired thrombolysis. Serum from five patients, (three 12 months after treatment and two with a high ASO titre) however, caused reduced fibrin lysis in the absence of raised streptokinase antibodies by either assay. Thus a normal IgG concentration >10 days after treatment does not necessarily ensure a normal fibrinolytic response. This discrepancy between antibody concentrations and impaired fibrinolysis has not been explained. One possibility is that there is a reduction in total antibody concentrations over time but maintenance of high affinity antibodies. A study of the concentrations of antistreptokinase immunoglobulin subclasses after treatment is being undertaken to examine this phenomenon.

To understand fully the clinical relevance of reduced in vitro fibrinolysis a comparison between the measurements made in this study and a clinical marker of effective thrombolysis is needed. At present no reliable non-invasive marker exists. In a recent study, however, Massel *et al* showed that the thrombolysis induced by streptokinase in an external jugular vein thrombosis model in rabbits was significantly impaired by giving streptokinase to the rabbits one month previously.[10] The pretreated animals had raised IgG antistreptokinase titres. This study suggests that there is a close correlation between in vitro resistance and impaired thrombolysis in vivo.

The results of our study suggest that up to 75% of patients treated once with streptokinase will be resistant to further treatment with streptokinase containing agents after two years. This suggests that the outcome from retreatment with streptokinase containing agents is likely to be unpredictable for a period beginning four to seven days after streptokinase doseage and lasting for more than two years. Other data suggest that this period may last for at least four years.[11] To identify patients who would benefit from repeated treatment with streptokinase, antibody concentrations or preferably fibrin plate lysis, could be measured routinely at regular intervals after first treatment. Such information, however, would have to be available immediately on admission with a further infarct. The only way to ensure this would be for the patients to carry this information themselves. Unfortunately, none of the tests used in this study could be performed rapidly enough at the bedside to be used on admission. We believe that titrating the dose upwards on the basis of the results of an in vitro test is an impractical approach that will only increase the antigenic load and the risk of an adverse immunological reaction.

In conclusion, streptokinase is likely to remain a first line agent for thrombolytic treatment in acute myocardial infarction. The prevalence of streptokinase resistance at first presentation is low unless there is evidence of recent streptococcal infection. The best predictor of streptokinase resistance is the fibrin plate lysis assay. Resistance can develop within 72 hours, although most patients seem to have a primary antibody response developing over seven to 10 days. All patients are resistant after 10 days and roughly 75% remain resistant after 24 months. Retreatment with thrombolytic agents containing streptokinase is inadvisable until the full clinical relevance and time course of streptokinase resistance is established.

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Evidence for oxidative stress in unstable angina

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Abstract

***Objective*—To determine whether unstable angina, which is characterised by recurring episodes of myocardial ischaemia and reperfusion, is associated with oxidative stress (that is, where there is an imbalance between oxidants, such as free radicals, which are in excess and antioxidants).**

***Design*—Between group comparison of patients with unstable angina, stable angina, and healthy controls.**

***Setting*—The coronary care unit and cardiac investigation ward of a regional cardiology centre.**

***Patients*—Twenty five consecutive patients admitted to the coronary care unit with unstable angina. Twenty five consecutive patients admitted to the cardiac investigation ward (patients with stable angina undergoing coronary angiography) were used as controls for the presence of atherosclerosis, drug treatment, and smoking habit. Thirty eight healthy controls (hospital staff and patients admitted for minor surgical procedures who were otherwise healthy) were also studied.**

***Main outcome measures*—Thiobarbituric acid related substances (TBARS) in plasma and plasma reduced thiol (PSH) as indicators of oxidative damage to lipids and proteins respectively were measured. Coronary angiography was performed in all patients with stable angina and roughly half of those with unstable angina.**

***Results*—Mean (SEM) plasma TBARS in unstable angina and stable angina were 9·95 (0·36) nmol/ml and 9·14 (0·28) nmol/ml respectively ($p = 0{\cdot}08$). Mean plasma TBARS in healthy controls were 8·09 (0·21) nmol/ml ($p < 0{\cdot}05$ compared with both angina groups). Mean (SEM) PSH concentration in unstable angina was 4·21 (9) nmol/ml and in stable angina was 4·85 (9) nmol/ml ($p < 0{\cdot}05$). Mean PSH in healthy controls was 5·64 (8) nmol/ml ($p < 0{\cdot}001$ compared with both angina groups). The extent of coronary artery disease, use of medication, and smoking habit were not significantly different between the angina groups.**

***Conclusions*—Biochemical indicators of oxidative stress are more abnormal in unstable than stable angina. This is in keeping with experimental evidence that episodes of ischaemia and reperfusion lead to generation of free radicals and toxic oxygen species and depression of endogenous antioxidant activity. The clinical significance of this finding remains to be determined, although, experimentally, free radicals and toxic oxygen species have adverse effects on myocardial contractile function, myocardial electrical stability, endothelial mediated vasodilatation, and coagulation.**

(*Br Heart J* 1992;68:454–7)

Free radicals and related toxic oxygen species have been implicated in a growing number of disease processes. Two mechanisms common to these processes are thought to lead to generation of free radicals and toxic oxygen species: these are the sequence of tissue ischaemia followed by reperfusion, and the activation of neutrophil nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and myeloperoxidase in the respiratory burst.[1–3] Endogenous antioxidant defences may also be depressed in these circumstances.[1–3] Where there is an imbalance between oxidant (eg, free radical) and antioxidant activity in favour of the oxidant oxidative stress is said to exist. Free radicals and associated toxic oxygen species are highly unstable chemically and immediately react with adjacent biomolecules to cause cellular and tissue damage.[1–3] In experimental models contractile and vascular endothelial injury can be caused in the heart by free radicals and toxic oxygen species.[3–5] Clinically, one common condition characterised by recurring episodes of myocardial ischaemia and reperfusion and neutrophil activation is unstable angina.[6] We have sought biochemical evidence of oxidative stress in patients with unstable angina. Concentrations of indicators of free radical damage to lipids (lipid peroxidation—that is, plasma thiobarbituric acid reactive substances (TBARS)) and proteins (thiol or sulphydryl group oxidation—that is, decreased plasma reduced thiol (PSH)) were measured.[1,7] Where there is an imbalance between oxidants (for example, free radicals) and antioxidants in favour of oxidants (where there is oxidative stress), lipid peroxidation is increased and protein thiols are decreased.[1,7]

Patients and methods

PATIENTS

Unstable angina

Twenty five consecutive patients admitted to the coronary care unit with a confirmed diagnosis of unstable angina were studied. Unstable angina was defined as an increase in frequency or severity or both of existing angina or recent onset angina requiring a stay in hospital. ST segment depression or T wave inversion had to be present on the electrocardiogram, and patients who had a rise in creatine kinase > 150 iu/l within 24 hours of admission were excluded from analysis. Patients with postinfarct angina were not recruited.

Stable angina

Twenty five consecutive patients with chronic stable angina and a positive exercise tolerance test (that is one associated with a > 1 mm ST segment depression by the end of stage III of the Bruce protocol) were recruited. All of these patients had been admitted for elective cardiac catheterisation under the care of one consultant cardiologist.

This study was approved by the West Ethical Committee of the Greater Glasgow Health Board and all patients gave informed consent before the study.

MEDICATION AND SMOKING HABIT

Oral and parenteral cardiac medication prescribed at the time of study were recorded: Smoking habit was also recorded.

CARDIAC CATHETERISATION

Patients with unstable angina were catheterised before discharge if their symptoms failed to settle on medical treatment, or if after discharge they had disabling angina despite medical treatment, or a positive exercise tolerance test. The coronary angiograms were reported independently of the biochemical analyses. A stenosis of >50% was taken as significant.

NORMAL CONTROLS

Healthy controls were recruited from the hospital staff and from patients admitted for minor surgical procedures.

BLOOD SAMPLES

All blood samples were taken at roughly 08.30 hours, after an overnight fast. The samples were taken from the patients with unstable angina the first morning after admission, and from the stable angina patients the morning after admission but before catheterisation. Samples were taken from an antecubital vein into chilled lithium heparin tubes and centrifuged immediately at 5·0°C. Plasma was separated and analysed the same day.

BIOCHEMICAL ASSAYS

Plasma concentrations of TBARS (malondialdehyde, MDA) were measured as already described.[8] Spectrophotometrical measurements of PSH were made with Ellmans reagent. The within and between assay coefficients of variance for these assays were: malondialdehyde 5% within and 6% between assays; PSH 2% within and 3% between assays.

STATISTICAL ANALYSIS

An unpaired t test was used to compare the three groups with Bonferroni's correction for multiple comparisons.

Results

CLINICAL CHARACTERISTICS

Healthy controls

Thirty eight controls (16 men) aged 21 to 65 years were recruited. None was on regular medication. Ten were current smokers.

Unstable angina

Patients aged 32 to 80 (mean 57 (SEM 2)) years, 15 men and 10 women were recruited. Nine were current smokers. In 80% treatment was with a β blocker, 76% with a nitrate, and 44% with a calcium channel blocker. Aspirin was taken by 84% and heparin by 28%. One patient eceived streptokinase and one patient had ventricular fibrillation (neither had had an infarction). One patient had a myocardial infarction more than 24 hours after admission. Twelve patients had a past myocardial infarction. Thirteen patients (52%) underwent cardiac catheterisation. Single vessel disease was present in 23% double vessel disease in 15%, and triple vessel disease in 46%; four (16%) patients had had coronary artery bypass grafting.

Stable angina

Results were analysed for 20 men and four women (one women patient had normal coronary arteries) aged 38–70 (mean (SEM) 58 (2)) years. Twelve patients were current smokers. The treatment for 71% was with a β blocker, 67% with a nitrate, 71% with a calcium channel blocker, and 42% were taking aspirin. Five patients had a past myocardial infarction. Twenty nine per cent of patients had single vessel disease, 13% double vessel disease, and 42% triple vessel disease; four (17%) had had coronary artery bypass grafting.

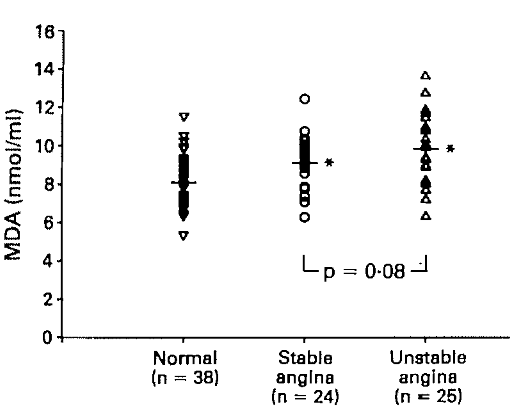

*Figure 1 Plasma concentrations of thiobarbituric acid related substances (malondialdehyde (MDA)) in healthy controls (normal), stable angina patients, and patients with unstable angina. Individual values are given with mean values indicated by a horizontal bar. *, $p < 0·02$ between angina groups and normal. Bracket denotes statistical comparison of the two angina groups.*

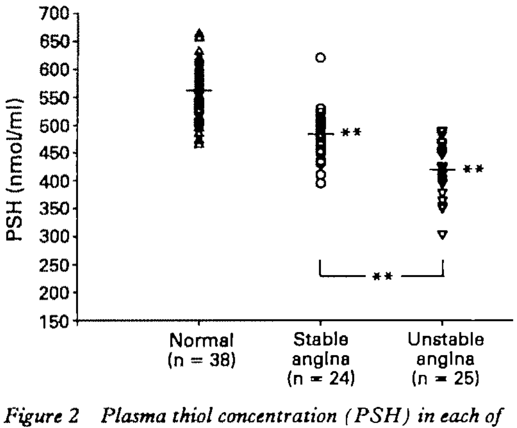

*Figure 2 Plasma thiol concentration (PSH) in each of the three groups as shown in fig 1. **, $p < 0·01$ for comparisons as in fig 1.*

BIOCHEMICAL MEASURES OF OXIDATIVE STRESS

TBARS (malondialdehyde)

Both groups of angina patients had significantly higher plasma malondialdehyde concentrations than the normal controls (fig 1). Mean plasma malondialdehyde seemed to be higher in patients with unstable angina compared with those with stable angina although this difference did not reach significance ($p = 0.08$).

PSH

In both groups of angina patients compared with controls PSH was significantly lower (fig 2), and PSH was also significantly lower in patients with unstable angina compared with those with stable angina (fig 2).

Discussion

Both groups of patients with coronary artery disease had abnormal indicators of oxidative stress in keeping with previous findings.[9 10] Interestingly, however, this abnormality was greatest in those patients with symptomatically overt ischaemia and could not be explained by such differences as extent of coronary disease or medication. This is in keeping with the belief that ischaemia and reperfusion, or neutrophil activation, or both cause generation of free radicals and other oxidants. Similar abnormalities in both markers measured in this study were noted in another study of myocardial ischaemia and reperfusion. In that study, Davies *et al* noted a rise in TBARS and a fall in PSH in patients with myocardial infarction who successfully reperfused after thrombolytic treatment.[11 12]

In our study the concentrations of the biochemical measures showed considerable overlap. This may reflect the fact that even stable angina patients have frequent episodes of recurring ischaemia (symptomatic or silent) and this may reduce the biochemical differences between the two angina groups. Decreased PSH has also been found in patients with stable angina and acute myocardial infarction.[9 13] Similarly, TBARS are increased after pacing induced ischaemia and during percutaneous transluminal coronary angioplasty in humans.[14 15]

What might the relevance of these findings be? It is known that abnormalities of wall motion may persist for days to weeks after an episode of unstable angina.[16] Such dysfunction seems to be the clinical correlate of the reversible experimental mechanical reperfusion injury that is apparently caused by the generation of free radicals and oxidants.[16] Oxidative stress may also provoke the arrhythmias that occur in a few patients with unstable angina (ventricular fibrillation occurred in one patient in this study).[4 5] Lipid peroxides, products of free radical damage to lipids, may cause damage to endothelial cells, decrease generation of vascular prostacyclin, and promote thrombosis.[5 9 10] All of these effects are potentially relevant and disadvantageous in patients with unstable angina.

LIMITATIONS

There are several limitations to this study. Methods of measuring lipid peroxides using thiobarbituric acid have been criticised on the basis of specificity. Nevertheless, this type of test remains an extremely sensitive one and is the most commonly used biochemical measure of oxidative stress. Abnormalities detected by us with the particular method used in this study have previously correlated well with other measures of redox state such as glutathione and superoxide dismutase;[17] also another marker, PSH, was used in this study to corroborate free radical damage.

A second limitation is that only a proportion of patients with unstable angina underwent cardiac catheterisation. It may therefore be argued that the extent of coronary disease in the whole unstable group could be greater than in the stable group. This would mean, however, that those in the unstable group who were not catheterised would have to have had more extensive coronary disease than those who were catheterised. This is highly unlikely as in our unit catheterisation is performed on the basis of either (*a*) failure to respond symptomatically to treatment or (*b*) the finding of a positive exercise tolerance test on medical treatment. It is probable, therefore, that those in the unstable group who were not catheterised had less rather than more extensive coronary disease. Thus it seems unlikely that the addition of non-catheterised unstable patients could have imbalanced the groups in terms of extent of coronary artery disease, in a way that would invalidate the results.

In summary we have shown that unstable angina is associated with abnormal plasma biochemical markers of oxidative stress. These findings support several recent findings in patients with other forms of myocardial ischaemia and reperfusion. The clinical relevance of these findings cannot be determined from this preliminary study. Unstable angina is, however, often associated with mechanical dysfunction and thrombotic coronary occlusion, both potential consequences of the generation of free radicals and toxic oxygen species. An association between abnormally high concentrations of indicators of oxidative stress and ventricular dysfunction or the occurrence of myocardial infarction would strengthen the case that biological oxidants including free radicals are clinically important.

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Modification of the circadian rhythm of onset of acute myocardial infarction by long-term antianginal treatment

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Abstract

***Objective*—To elucidate the mechanism of the circadian pattern of onset of acute myocardial infarction by examining the effects of prior antianginal treatment upon it.**

***Design*—Retrospective analysis of clock time of the onset of acute myocardial infarction by linear modelling to define the circadian distribution of hourly onset rates and to examine the deviation of treated groups of patients from this distribution.**

***Setting*—Coronary care unit in a general hospital taking unselected acute admissions from a district of 0·9 million people.**

***Patients*—A series of 2231 patients with confirmed acute myocardial infarction.**

***Results*—A major 24 h cycle and smaller 12 h and 6 h cycles were present in patients not taking antianginal medication. Onset rates varied twofold over the day, with maxima around 10.00 am and 10.00 pm. This pattern was unchanged in patients on prior treatment with regular nitrates, but in those who had been taking a β blocker or a calcium antagonist the 24 h cycle was absent.**

***Conclusions*—These results are best explained by the shared property of β blockers and calcium antagonists to reduce blood pressure and myocardial oxygen demand. The mid-morning peak of the onset of myocardial infarction is attributable to the physiological increase in sympathetic drive and cardiac work at that time. The data are not consistent with the triggering of the 24 h periodicity by fluctuations in coronary tone or haemostatic activity.**

(*Br Heart J* 1992;68:458–61)

Acute myocardial infarction occurs as the end result of two sequential processes—coronary atherosclerosis and thrombotic occlusion. The risk factors for these two processes are unlikely to be the same though they cannot be distinguished by conventional epidemiological studies. A clear understanding of the trigger for acute thrombotic occlusion would provide scope for pharmacological primary prevention. A promising approach to the mechanism of the occlusive event is offered by the observation that the time of onset of acute myocardial infarction is not randomly distributed but shows a strong circadian rhythm with its major peak in the mid-morning and a minor peak in the late evening.[1,2] A similar pattern has also been reported for sudden cardiac death.[3] Possible explanations for this periodicity include physiological fluctuations in blood pressure,[4] sympathoadrenal activity,[5] platelet aggregability,[6] or coronary tone.[7]

Evidence of modification of the circadian pattern by prior drug therapy would give insight into its mechanism. The use of observational data to identify drug effects requires particular care to control for confounding in the analysis.[8] Muller *et al* found no circadian pattern of onset in patients entering the MILIS (Myocardial Infarction Limitation Intervention Study) trial with acute myocardial infarction who had been taking β blocking drugs before admission but the statistical power was only 48% and concurrent use of other antianginal agents was not excluded.[1] Willich *et al* also found no circadian periodicity of onset among patients with myocardial infarction entering the ISAM (intravenous streptokinase in acute myocardial infarction) trial who had been taking a β blocker but they did observe a significant morning peak of onset among all trial entrants and in a subgroup who had been taking a calcium antagonist.[9] For the whole UCSD (University of California at San Diego) Collaborative Database of 4796 patients there were two peak times of onset, the larger between 6.00 am and noon and the smaller between 6.00 pm and midnight; in the subgroup who had been taking a β blocker the two peaks were of equal size.[2] The problem of co-prescribing of antianginal drugs has not been addressed. In both the MILIS[1] and the ISAM[9] reports less than half the screened patients were included in the analysis of periodicity, so that selection bias could have arisen.

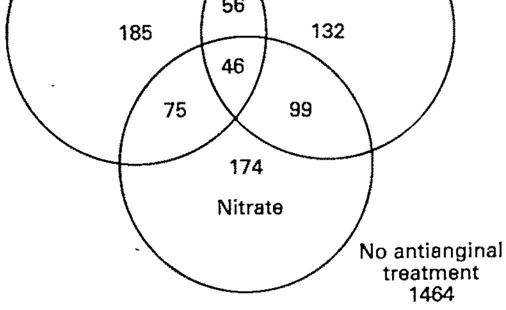
The present study was undertaken to examine the temporal distribution of the onset of acute myocardial infarction in a consecutive series of patients and to investigate the separate effects upon it of prior treatment with β blockers, calcium antagonists, or nitrates. The important hypothesis to be tested is not whether patients in these treatment subgroups show a circadian pattern of onset of infarction, but whether the subgroups deviate significantly from the circadian pattern shown by patients not on prior chronic treatment with antianginal drugs. The first step in the present study was therefore to develop the best-fit mathematical model for the temporal distribution of onset of myocardial infarction in a large series of untreated patients. Treatment effects were then examined in groups of patients who had been receiving one or more antianginal drugs at the time of onset of acute myocardial infarction. The term "antianginal drug" refers here to β blockers, nitrates (long-acting oral or transdermal preparations only), and calcium antagonists whether they had actually been prescribed for angina or for another indication. To avoid confounding of the drug effects by coprescription of more than one class of antianginal drug, their separate effects on circadian periodicity were identified by linear modelling.

Patients and methods

The patients included in the study were admitted with acute myocardial infarction to the coronary care unit of Leicester Royal Infirmary between January 1987 and September 1991. The diagnosis was based on the presence of at least two of the following: typical cardiac pain of at least 20 minutes' duration unrelieved by rest or buccal nitrates; evolving electrocardiograph changes of infarction; and a rise in the serum creatine kinase concentration to above twice the upper limit of the laboratory reference range. For each patient a detailed record of history, medication on admission, and other clinical data was completed on entry by medical staff and stored on computer without knowledge of the hypothesis to be tested. The clock time of onset of the symptoms of myocardial infarction was derived from the clock time of admission and the duration of symptoms as reported on admission. The clock time of onset of symptoms could not be estimated in 69 (3·0%) of 2300 consecutive patients with confirmed acute myocardial infarction. The remaining 2231 patients formed the study group. Their mean age was 63 years. Figure 1 shows the subgroups by treatment. The calcium antagonists being used were examined by a random sampling of 100 sets of case-notes in this subgroup; 83% were taking a dihydropyridine (most commonly nifedipine), 15% diltiazem, and 2% verapamil. The number of patients (8·6%) taking a non-steroidal anti-inflammatory drug regularly (including aspirin) was too small for separate analysis.

The data were formed into a contingency table of the hour of day of onset by level of drug therapy with the cells of the table containing the number of individuals. To form the table the times of onset were rounded to the nearest hour, the boundaries being the surrounding half hours. Initially the levels of drug treatment were classified as no drug therapy, β blockers (BB) only, calcium antagonists (CA) only, nitrates (NI) only, BB + CA, BB + NI, CA + NI, and BB + CA + NI. We fitted log linear models to this table using the statistical package GLIM[10] with a Poisson error structure. The clock time of onset was entered into the model in the form of paired sine and cosine transformations representing the harmonic components. The initial model (model 1) included harmonic terms up to the fourth order (24, 12, 8, and 6 h cycles) with levels of drug treatment. The model allowed a different baseline for each category of drug treatment and contained interaction terms between level of drug treatment and each sine and cosine term. Each level of drug treatment was therefore represented by a different wave form. From this model the effect of each of the harmonic components of the model was tested by dropping terms if the resulting change in deviance (with a χ^2 distribution) was non-significant at the 1% level. The overall fit of the final model (model 2) formed by this step-down process was assessed by plots of the standardised residuals[11] against the fitted values, time of onset, and level of treatment. From model 2 two further hypotheses were tested. The first was that any drug or combination had the same effect on the wave form of time of onset (the constant term representing the baseline being unaffected). The second hypothesis tested the equality of the constant term for any drug class or combination of drug classes.

Figure 1 Patient subgroups defined by antianginal treatment being taken prior to the onset of acute myocardial infarction.



Results

Figure 2 shows the raw data for the circadian distribution of onset of symptoms of myocardial infarction. Data for patients on no prior antianginal treatment (n = 1464) and those on any regular antianginal treatment (n = 767) are plotted separately.

Model 1, containing a constant term and four pairs of sine and cosine terms for each level of drug treatment, had a deviance of 11·0 on 120 degrees of freedom (df). Neither the fourth order harmonic ($p = 0{\cdot}75$), third harmonic ($p = 0{\cdot}51$), nor second harmonic ($p = 0{\cdot}81$) were significantly different for the different levels of drug treatment. Checks on the contribution of the second, third, and fourth harmonic terms to the model showed that the third harmonic ($p = 0{\cdot}23$) could be dropped but both the second ($p < 0{\cdot}0001$) and the fourth harmonics ($p = 0{\cdot}004$) added significantly to the model. Model 2, therefore, had a different baseline level and first order harmonic for each class of drug together with a second and fourth order harmonic that were the same for all levels of drug treatment. The overall fit of this model (model 2) was good with a deviance of 146.4 on 164 df and was supported by plots of the standardised residuals against the fitted values, time of onset, and level of drug treatment.

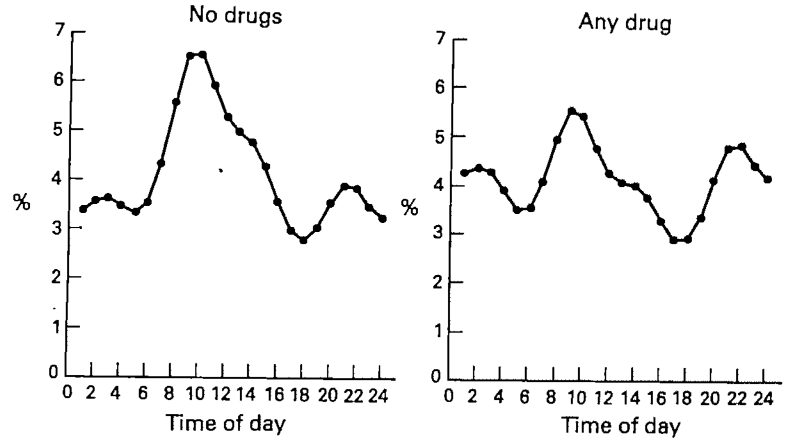


Figure 2 Observed distribution of time of onset of symptoms of myocardial infarction: (A) for patients not taking antianginal drugs (n = 1464) and (B) for patients on any antianginal drug treatment (n = 767).

Table Coefficients and standard errors of the terms in the final model (model 3)

Term in the model	*Coefficient (SE)*
Constant + :	
No drug	4·08 (0·03)
BB	2·03 (0·07)
CA	1·69 (0·09)
NI	1·96 (0·08)
BB + CA	0·83 (0·13)
BB + NI	1·12 (0·12)
CA + NI	1·40 (0·10)
BB + CA + NI	0·64 (0·15)
Cosine 1st order harmonic:	
No drug	−0·24 (0·04)
Any drug	0·01 (0·05)
Sine 1st order harmonic:	
No drug	0·11 (0·03)
Any drug	0·09 (0·05)
Cosine 2nd order harmonic	0·14 (0·03)
Sine 2nd order harmonic	−0·13 (0·03)
Cosine 4th order harmonic	−0·11 (0·03)
Sine 4th order harmonic	0·01 (0·03)

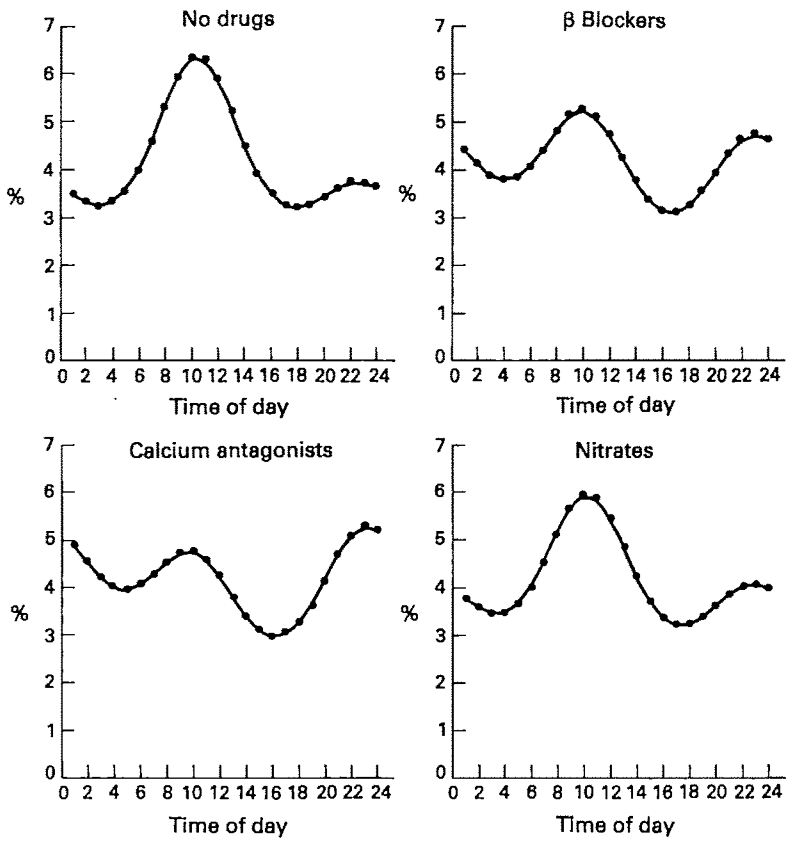


Figure 3 Fitted harmonic regressions (model 3) of the distribution of time of onset for patients (A) not taking antianginal drugs, (B) taking blocker, (C) taking a calcium antagonist, (D) taking nitrates regularly.

The next stage in the modelling process was to test the equality of the harmonic terms in those patients who had been receiving any regular antianginal treatment. The fit of this model (model 3) was not significantly worse than that of model 2 ($p = 0·68$). The test of the second hypothesis, that the constant term was identical for all those on drug treatment, was rejected ($p < 0·0001$). A further model was fitted which allowed the constant term to be identical for combinations of two or more drugs only, but this again gave a significantly poorer fit to the data ($p < 0·0001$). Plots of standardised residuals for model 3 showed no evidence of non-random scatter, and the overall deviance of 156·0 on 176 df demonstrated that the model fitted the data well. The table shows the coefficients of the terms in Model 3 and their standard errors.

Figure 3 shows plots of the fitted distribution of onset throughout the 24 h, using model 3, for patients on no drug treatment and taking each class of anti-anginal drug. The clear circadian pattern seen in the patients on no drug treatment was unaffected by prior use of nitrates; in contrast, the dominant 24 h cycle with its peak around 10.00 am was abolished by β blockers and calcium antagonists though in each case a residual 12 h cycle was clearly apparent.

Discussion

Timing the onset of acute myocardial infarction from the history has been shown to correlate very well with back-extrapolation from the rise in cardiac enzymes.[1 9] Since all but 3% of patients with confirmed acute myocardial infarction were included in the analysis, the only factor that might have produced selection bias is death before the patient reached hospital. This is unlikely because out-of-hospital sudden cardiac deaths have been shown to have a similar harmonic distribution to that seen in survivors reaching hospital.[3]

The circadian pattern reported here has its maxima and minima within an hour of the "population rhythm" of the onset of acute myocardial infarction described by Muller *et al.*[1] The ISAM data[9] generally accord with our results though spectral analysis of the ISAM data showed only one (24 h) cycle. In addition to the well recognised dominant 24 h periodicity, we saw the smaller 12 hour cycle noted in some studies of acute myocardial infarction as a late evening peak,[1 2 12] and an additional minor 6 h cycle not previously described.

The main interest of the present study concerns the treatment subgroups. This type of analysis raises important issues of statistical inference that have usually not been adequately addressed. Firstly, the arbitrary division of the day into a small number of intervals to form a contingency table is insensitive and may introduce bias if data-derived. Use of hourly rates as dependent variables in a regression analysis has clear advantages. Secondly, statistical power will inevitably decrease as smaller subgroups within the whole sample are examined and the form of the null hypothesis will determine the consequences of a type II error. If the null hypothesis is that of a uniform distribution of cases over time, a type II error will lead to the incorrect conclusion that in contrast to the whole sample the subgroup lacks a circadian pattern. The appropriate null hypothesis is that the subgroup does not deviate from the best-fit circadian pattern previously identified in the whole sample: a type II error will then be conservative and will not lead to the same false inference. Thirdly, treatment subgroups have to be examined in such a way as to control for the common co-prescription of major drug classes that was clearly seen in this data set. These analytical problems are best handled by the technique of linear modelling, specifying the Poisson error distribution appropriate to count data.

Although the mechanisms driving the 12 h and 6 h cycles are unknown, there are three plausible triggers to account for the 24 h cycle which causes the mid-morning peak and is suppressed by prior treatment with a β blocker or calcium antagonist. There is evidence for suitably timed circadian variations in haemodynamic function,[4,13] resulting in increased cardiac work; in coronary tone,[14] which could precipitate plaque rupture;[6,15,16] and in haemostatic function, predisposing to acute occlusion of an atheromatous coronary artery.[6] Our data on the classes of antianginal drugs strongly support the first of these proposed mechanisms. β Blockers and calcium antagonists by their antihypertensive and negatively inotropic effects will control the extra myocardial oxygen demand imposed by the known morning increase in sympathetic drive, blood pressure and heart rate.[13] The observed abolition of 24 h periodicity of onset by β blockers but not by regular nitrates indicates that circadian fluctuation in coronary tone (which has been described in patients with unstable angina[17]) does not cause the 24 h cycle of myocardial infarction, despite the evidence that coronary spasm can precipitate thrombotic occlusion by causing plaque rupture.[7,15]

Transient myocardial ischaemia detected by continuous ambulatory monitoring of patients with coronary artery disease shows both 24 h and 12 h periodicities with maxima around 10.00 am and 9.00 pm.[18,19] The morning peak is suppressible both by atenolol[18] and by nifedipine[19]; long-term nitrate treatment does not seem to have been investigated in this context. The close similarity of transient ischaemia and acute myocardial infarction in terms of their chronobiology and its modification by treatment suggests that the same triggering mechanism operates.

The present study design does not allow any direct measurement of the effect of prior drug treatment on the overall risk of myocardial infarction. A clearer understanding of the process whereby stable coronary artery disease progresses to acute occlusion may nevertheless guide treatment strategies for angina. These observational data give indirect evidence for a protective action of β blockers and calcium antagonists that is not shared by long-acting nitrates. Definitive proof would require randomised trials of an unprecedented size and duration.

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Early diagnosis of acute myocardial infarction by a newly developed rapid immunoturbidimetric assay for myoglobin

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Abstract

***Objective*—To evaluate a rapid immunoturbidimetric assay for myoglobin and to investigate its clinical usefulness in the early detection of acute myocardial infarction.**

***Design*—Prospective study. Immunoturbidimetrically determined myoglobin concentrations were compared with radioimmunoassay results obtained with the same blood samples. The diagnostic performance of myoglobin determination was compared with creatine kinase and creatine kinase MB activity (current standard of routine diagnosis).**

***Settings*—Part 1: coronary care unit. Part 2: emergency room in a university hospital.**

***Patients*—Part 1: 30 patients with acute myocardial infarction admitted not later than four hours (median two hours) after the onset of symptoms. Part 2: 126 patients admitted to the emergency room with chest pain not caused by trauma (51 cases of acute myocardial infarction, 51 cases of angina pectoris, and 24 cases of chest pain not related to coronary artery disease).**

***Interventions*—Part 1: routine treatment including intravenous thrombolytic treatment (28 patients). Part 2: routine emergency treatment without thrombolytic treatment.**

***Main outcome measures*—The analytical quality of the immunoturbidimetric myoglobin assay and a comparison between the myoglobin assay and creatine kinase and creatine kinase MB for diagnostic sensitivity and performance.**

***Results*—The immunoturbidimetric myoglobin assay was fast and convenient and gave myoglobin determinations of high analytical quality. The concentration of myoglobin increased, peaked, and returned to the reference range significantly earlier than creatine kinase ($p \leqslant 0{\cdot}0001$) and creatine kinase MB ($p \leqslant 0{\cdot}0002$). Before thrombolytic therapy was started the diagnostic sensitivity of myoglobin was significantly higher than that of creatine kinase MB activity 0–6 h after the onset of chest pain and significantly higher (0·82 *v* 0·29) than creatine kinase 2–4 h after the onset of chest pain. In almost all patients (92%) plasma myoglobin concentrations were increased 4–6 h after the onset of chest pain.**

***Conclusion*—Myoglobin was more sensitive in detecting early myocardial infarction than creatine kinase and creatine kinase MB activity. Immunoturbidimetric myoglobin measurements could be useful in the early evaluation of patients with suspected myocardial infarction because this assay takes less than two minutes.**

(*Br Heart J* 1992;68:462–8)

Apart from the patient who presents with classic symptoms and typical electrocardiographic changes, the early detection of acute myocardial infarction based on conventional clinical and electrocardiographic findings alone is difficult.[1] Most patients with acute myocardial infarction show some electrocardiographic changes, but these changes are diagnostic in only about one third of patients with acute myocardial infarction when they present at the emergency room.[2-4] The use of thrombolytic therapy for myocardial salvage reinforces the need for early and rapid identification and confirmation of acute myocardial infarction within four to six hours after the onset of the infarct-related symptoms.[5] Creatine kinase and creatine kinase MB activity, which are the most frequently assayed biochemical markers in emergency laboratories, do not rise in serum until the fourth to eighth hour after the onset of chest pain,[6] and so are not sensitive enough for diagnosis during the early stages of acute myocardial infarction. Myoglobin, by contrast, is an early sensitive marker of myocardial cell injury.[7-10] Until recently radioimmunoassay and latex agglutination were the two techniques available for myoglobin determination. Radioimmunoassays are time consuming and therefore not suited for use in emergency room laboratories. Latex agglutination is a rapid test but the results are only semi-quantitative estimations of serum myoglobin concentrations. Under optimal laboratory conditions, the latex test is a reliable method of estimating myoglobin concentrations. Performed occasionally by a technical assistant on duty or when used as a bedside test, however, its results correlated rather poorly with the radioimmunoassay results.[11] So, though myoglobin is known to be an early sensitive indicator of acute myocardial infarction and to be a reliable non-invasive predictor of the outcome of therapeutic reperfusion,[12 13] it has not been widely used in the early evaluation of patients with suspected acute myocardial infarction.

We have evaluated a rapid, quantitative immunoturbidimetric myoglobin assay in the early detection of acute myocardial infarction.

Patients and methods

PATIENTS

The study was carried out in two parts.

Part 1

This part of our study was performed to confirm the differences in the time courses of myoglobin, creatine kinase MB, and total creatine kinase activity in plasma after acute myocardial infarction and to establish a correlation between myoglobin concentrations measured by radioimmunoassay and by immunoturbidimetry. Thirty consecutive patients with subsequently confirmed myocardial infarction (22 men and eight women) aged 40–83 years (median 61 years) presented to the hospital coronary care unit within four hours after the onset of symptoms and gave informed consent for extra blood samples to be drawn. Patients presenting to the coronary care unit more than four hours after the onset of symptoms were excluded, because at this stage of acute myocardial infarction there is a high probability of increased creatine kinase and creatine kinase MB activity and an increased myoglobin plasma concentration. The median time to admission was two hours (range 30–240 minutes). All patients subsequently proved to have sustained an acute myocardial infarction (27 Q wave and three non-Q wave myocardial infarctions: 12 anterior and 18 inferior wall infarctions). Myocardial infarction was diagnosed independently by two cardiologists according to the World Health Organisation criteria[14] based on the patient's clinical history and symptoms, electrocardiographic abnormalities, and serum enzyme findings and without knowledge of the myoglobin results. Treatment was determined by the clinical circumstances. Fifteen patients were given intravenous streptokinase (1·5 million units in 60 minutes), two patients were given intravenous urokinase (2 million units in 10 to 15 minutes), and 11 patients were given intravenous alteplase (initial bolus of 10 mg, followed by 50 mg during the first hour and 20 mg each during the second and third hour after admission). Two patients were not given thrombolytic treatment because of contraindications. All patients additionally received routine coronary care and were treated with intravenous heparin, aspirin, nitrates, occasionally β blockers, and antiarrhythmic drugs as needed. Peripheal venous blood samples were collected from an indwelling forearm catheter or by venepuncture before treatment in the coronary care unit. Samples were collected hourly for the first 10 hours, then at 12, 16, 20, 24, 32, 40, 48 hours after admission, and thereafter daily until biochemical markers returned to normal. Patient care requirements occasionally prevented a sample being taken.

On the basis of recent findings,[15] coronary angiography was performed only selectively usually several days after admission. So the occurrence of reperfusion in Q wave infarction could not be observed directly by coronary angiography but had to be inferred from less definitive non-invasive criteria. It is well established, both clinically[12 16–18] and experimentally,[19 20] that reperfusion in Q wave infarction results in a more rapid increase in creatine kinase and myoglobin and in early peaks of both proteins. Early reperfusion was assumed to have occurred (95% probability of correct classification) if there was both a myoglobin peak within seven hours and a creatine kinase peak within 16 hours after the onset of chest pain.[13] Eighteen of 25 patients with Q wave myocardial infarction given thrombolytic therapy were classified as "reperfused early".

Part 2

In the second part of the study we evaluated the immunoturbidimetric myoglobin determination as a rapid screening assay for myocardial infarction in patients with chest pain presenting to the emergency room. One hundred and twenty six consecutive patients in the hospital's department of internal medicine with chest pain as their major symptom were investigated. The study population did not include patients with chest contusion or injured patients. Fifty one patients subsequently proved to have sustained an acute myocardial infarction (median delay from the onset of chest pain to admission 2·25 h, range 0·5–14·5 h), which was diagnosed by two cardiologists according to the WHO criteria given earlier. Twenty six patients sustained a Q wave acute myocardial infarction (median delay 1·75 h, interquartile range 1–3·5 h) and 25 a non-Q wave acute myocardial infarction (median delay 4 h, interquartile range 1–7·15 hours). Fifty one patients presented with angina pectoris. A further 24 patients had chest pain not related to coronary artery disease (three cases of supraventricular tachycardia, four pneumonia with pleurisy, one obstructive pulmonary disease, four musculoskeletal disorders, three pericarditis, six pulmonary embolism, two oesophagitis, and one case of hypertensive crisis). In these patients a single blood sample was drawn immediately after presentation to the emergency room. All patients received routine emergency treatment. All patients with acute myocardial infarction were transferred to the coronary care unit before the start of thrombolytic therapy. None of these patients with acute myocardial infarction had been given thrombolytic agents before admission to the hospital.

LABORATORY ANALYSIS

Blood collection

Blood was collected in tubes coated with EDTA. Creatine kinase and creatine kinase MB activities were assayed immediately after collection. Blood samples for the measurement of myoglobin concentrations were centrifuged immediately and the plasma subsequently frozen and stored at -20°C until determination. Under these conditions myoglobin could be assayed within at least four weeks (maximum period of storage) after collection without any decline in concentration.

Creatine kinase and creatine kinase MB activity

Total creatine kinase and creatine kinase MB activities were measured (25°C) with N-acetylcysteine activated, optimised ultraviolet test kits obtained from Merck (Darmstadt, Germany). Creatine kinase MB activity was measured by means of immunoinhibition based on the presence of inhibiting creatine kinase M antibodies. According to the manufacturer's recommendations, a total creatine kinase activity of 70 U/l for women and 80 U/l for men was used as the upper limit of the reference interval. For creatine kinase MB activity the reference range goes up to 10 U/l. Creatine kinase MB activities of >10 U/l and an increase of $>6\%$ in total creatine kinase activity were assumed to indicate myocardial muscle cell damage.

Myoglobin

Myoglobin radioimmunoassay—Myoglobin was determined by a commercially available radioimmunoassay (Byk-Sangtec, Dietzenbach, Germany). The manufacturer's upper limit of the reference interval is 80 µg/l.

Immunoturbidimetric myoglobin assay—A myoglobin assay (Turbiquant myoglobin, Behringwerke AG, Marburg, Germany) for use with the Behring Turbitimer analyser was used for rapid immunoturbidimetric determination of myoglobin concentrations in plasma.[21] This assay is based on polystyrene particles coated with rabbit anti-human myoglobin antibodies. In an immunochemical reaction these particles form agglutinates with the myoglobin contained in serum or plasma. The increase in turbidity is measured photometrically.[22] Quantitative results are available about a minute after the start of the assay. The detection limit of the assay is 50 µg/l and the measurement range 50–650 µg/l. The concentrations of myoglobin in EDTA plasma from 100 apparently healthy subjects (blood donors with no history of cardiovascular diseases) (41 men and 59 women aged 19–65 (median 44 years)) were measured by this new method to obtain a reference interval calculated by nonparametric determination of percentiles.

DATA ANALYSIS

Median, interquartile range, and percentiles were calculated to describe continuous variables. The association between continuous variables was analysed by the Spearman rank correlation test. The Wilcoxon signed rank test and χ^2 test (or Fisher's exact test where appropriate) were used for between group comparisons. Confidence intervals were calculated according to the method of Gardner and Altman.[23] A p value of $<0·05$ was regarded as significant. Bonferroni adjustment was used for comparison of more than two groups. Sensitivity, specificity, efficiency, positive and negative predictive values, likelihood ratio, and Youden index (sensitivity + specificity − 1) were calculated to describe the performance of myoglobin, creatine kinase, and creatine kinase MB activity in the early diagnosis of myocardial infarction in patients in the emergency room.[24–26]

Results

IMMUNOTURBIDIMETRIC ASSAY FOR MYOGLOBIN

Reference interval of myoglobin concentrations in plasma by the immunoturbidimetric assay

Figure 1 shows the distribution of myoglobin concentrations in 100 healthy individuals. In most the myoglobin concentration was below the detection limit of the assay. The upper limit of the reference interval (cut off value), calculated as the 97·5% percentile, was 70 µg/l. The age or sex of the reference subjects did not influence the myoglobin concentrations. The correlation coefficient between myoglobin concentrations and age was 0·08. There was no significant (p = 0·27) difference between myoglobin concentrations in men and women.

Correlation with radioimmunoassay method

Myoglobin was simultaneously determined by both methods in serial blood samples taken from 30 patients with acute myocardial infarction. There was a good correlation between the immunoturbidimetric assay and radioimmunoassay for myoglobin time courses of individual patients with myocardial infarction. The median correlation coefficient was 0·96 (interquartile range 0·91–0·97). However, values obtained by the immunoturbidimetric assay were usually lower than those obtained by radioimmunoassay.

Interference

Rheumatoid factors (tested for a concentrations up to 1260 IU/ml) did not interfere with the assay. The myoglobin assay is usually not disturbed by icteric, haemolytic, and lipaemic samples. However, if the absorbance of the sample is too high before the reaction starts (for example, because of strong absorption caused by haemolysis or hypertriglyceridaemia), the analyser generates a warning message and the assay cannot be done. Such samples can be

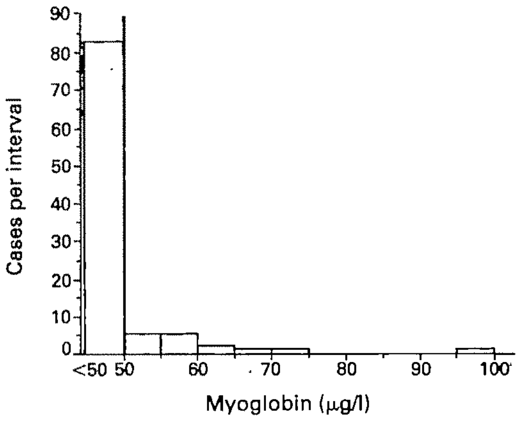

Figure 1 Plasma concentrations of myoglobin in 100 healthy volunteers. The bars represent the number of cases including the lowest value of each interval. The detection limit of the assay is 50 µg/l (bold line).

retested after manual predilution. Hypertriglyceridaemic samples can be also clarified by centrifugation (10 min at approximately 15 000 *g*) and retested.

Reproducibility

The calculation of the coefficients of variation for patients' and control samples was based on 20 measurements each. The intraassay coefficients of variation ranged from 2·2% to 6·8% and the interassay coefficients of variation from 5·9% to 11·7%. The highest coefficients of variation were found for samples with low myoglobin concentrations.

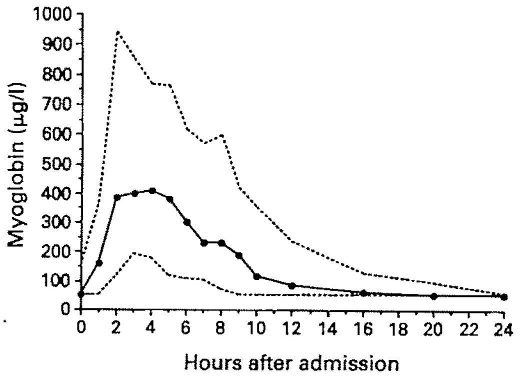

Figure 2 Time course of plasma concentrations of myoglobin in 30 patients with acute myocardial infarction (27 Q wave, three non-Q wave) presenting within four hours after the onset of symptoms. Data are given as median (solid line) and interquartile ranges (broken lines). Twenty five patients with Q wave acute myocardial infarctions were treated with intravenous thrombolytic agents, resulting in early reperfusion in 18.

TIME COURSES OF MYOGLOBIN, CREATINE KINASE, AND CREATINE KINASE MB ACTIVITY IN MYOCARDIAL INFARCTION

Figure 2 summarises the time courses of myoglobin concentrations of 30 patients with myocardial infarction. Thrombolytic therapy resulted in early reperfusion in 18 of 25 patients with Q wave infarction. The time courses of myoglobin, creatine kinase, and creatine kinase MB activities in patients with non-Q wave myocardial infarctions resembled those of patients with Q wave myocardial infarctions with early reperfusion. Table 1 shows the criteria describing the release kinetics of myoglobin, creatine kinase, and creatine kinase MB activities. An abnormal increase, the peak concentration, and return into the reference range occurred significantly earlier for myoglobin than for creatine kinase ($p \leqslant 0{\cdot}0001$) and creatine kinase MB activity ($p \leqslant 0{\cdot}0002$). The median difference between the first appearances of myoglobin and creatine kinase and the first appearances of myoglobin and creatine kinase MB was one hour each (95% CI 1–2 h). In these patients the diagnostic sensitivity of myoglobin was significantly ($p < 0{\cdot}05$) higher than that of both creatine kinase and creatine kinase MB activity at 3·5 and four hours after the onset of symptoms (fig 3). The diagnostic sensitivity of myoglobin was 0·5 (50%) 3·4 hours after the onset of symptoms—a value that creatine kinase activity only reached after 4·8 hours and creatine kinase MB after five hours respectively (table 1). All patients had increased myoglobin concentrations (100% sensitivity) at six hours and increased creatine kinase and creatine kinase MB activities at 12 hours after the onset of chest pain (fig 3). The median peak values of myoglobin, creatine kinase, and creatine kinase MB were attained early after admission because of the high percentage (72%) of patients with Q wave myocardial infarction who achieved early reperfusion. The magnitude of increase (calculated as the peak value divided by the cut off value) of myoglobin was significantly (table 1) greater than for creatine kinase activity ($p = 0{\cdot}0007$) and creatine kinase MB activity (0·0001). The period when plasma concentrations of myoglobin were increased after acute myocardial infarction that allowed a diagnosis based on increased biochemical markers was significantly shorter than that of creatine kinase ($p = {\cdot}0001$) and creatine kinase MB activity ($p = 0{\cdot}0002$). The correlation coefficient between peak values of myoglobin and creatine kinase was 0·69 ($p = 0{\cdot}0002$) and between myoglobin and creatine kinase MB it was 0·68 ($p = 0{\cdot}0002$).

DIAGNOSTIC PERFORMANCE OF MYOGLOBIN, CREATINE KINASE, AND CREATINE KINASE MB ACTIVITY WHEN USED TO DETECT ACUTE MYOCARDIAL INFARCTION IN EMERGENCY ROOM PATIENTS WITH CHEST PAIN

In this group the prevalence of myocardial infarction was 0·4 (pretest odds 0·68). The median creatine kinase activity in patients with acute myocardial infarction (n = 51) was 68 U/l (interquartile range 47–142 U/l), the median creatine kinase MB activity was 10 U/l (interquartile range 4–12 U/l). In these patients myoglobin concentrations ranged from <50 µg/l to 2990 µg/l. Eighteen patients with acute myocardial infarction had myoglobin concentrations below the detection limit (50 µg/l) of the immunoturbimetric assay. The median creatine kinase activity in patients with angina pectoris was 37 U/l (interquartile range 26–68 U/l), the median creatine kinase MB activity was 4 U/l (interquartile range 4–6 U/l). In this group (n = 51) myoglobin concentrations ranged from <50 µg/l to 72·6 µg/l and were <50 µg/l in 43 cases. In patients with chest

Table 1 Release kinetics of myoglobin, creatine kinase (CK), and creatine kinase MB activity in 30 patients with acute myocardial infarction (median (95% CI))

	CK MB activity	*CK activity*	*Myoglobin*
Cut off value	10 U/l	70 U/l	70 µg/l
Time to first increased plasma values (h)	5 (4–6)	4·8 (3·5–5·3)	3·4 (2·8–4·0)
Time to peak (h)	11·3 (11–14·3)	13 (11·5–15·8)	5·9 (4·5–7·5)
Return to normal (h)	53 (36·3–76)	74 (50–96)	21·5 (17·8–26·0)
Period of increased plasma values (h)	50 (32·3–71·8)	68 (46–78)	17 (12·8–23·0)
Magnitude of increase*	4·5 (3·5–7·7)	7 (4·3–12)	9·3 (5·5–23·6)

The onset of symptoms (chest pain) was the reference point for the calculation of first appearance in blood, time to peak value, and time of return to normal.
*Peak value divided by cut off value. Twenty five patients with Q wave acute myocardial infarctions were given intravenous thrombolytic treatment, which resulted in early reperfusion in 18.

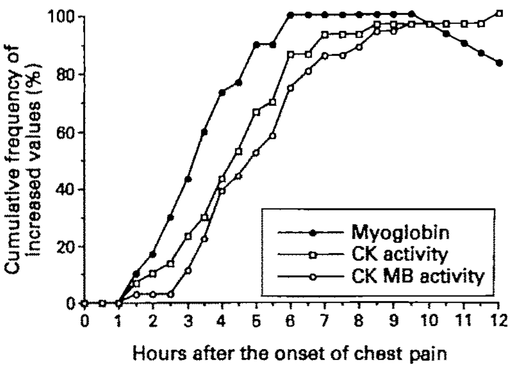

Figure 3 Diagnostic sensitivity of myoglobin, creatine kinase (CK), and creatine kinase MB activity during the first hours after the onset of symptoms (with patients receiving thrombolytic treatment included) in the 30 patients shown in fig 2. Symbols represent the number of increased values (%) including the lowest value of each time classification (30 minute intervals).

pain not related to coronary artery disease the median creatine kinase activity was 33 U/l (interquartile range 15–59 U/l) and the median creatine kinase MB activity was 4 U/l (interquartile range 4–5 U/l). Myoglobin concentrations measured in the same blood samples ($n = 24$) ranged from <50 µg/l to 162 µg/l and were <50 µg/l in 23 patients. Figure 4 shows the influence of the cut off value on the sensitivity, specificity, and Youden index of myoglobin in the discrimination between acute myocardial infarction and non-acute myocardial infarction in patients presenting to the emergency room with symptoms that suggested myocardial infarction. The myoglobin cut off value that yielded the highest Youden index lay somewhere below the detection limit of the immunoturbidimetric assay. The myoglobin cut off value of 70 µg/l (established in healthy blood donors) gave good sensitivity (0·45) and specificity (0·91). Table 2 shows various indices of performance of the diagnostic tests. For the calculations presented in table 2 we used either the cut off values recommended by the manufacturer (creatine kinase and creatine kinase MB activity) or our own cut off values established in healthy blood donors (myoglobin). Twenty two (43%) of the patients with acute myocardial infarction were admitted to the hospital either within two hours or more than six hours after the onset of chest pain.

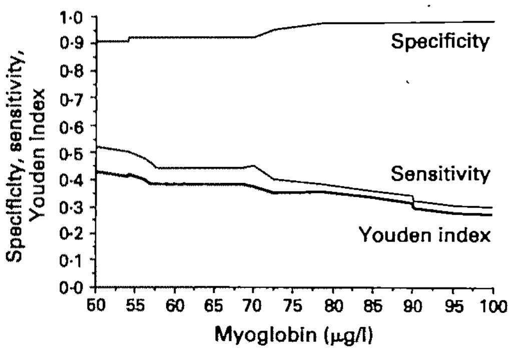

Figure 4 Diagnostic performance when different cut off plasma concentrations of myoglobin were used to detect acute myocardial infarction in 126 patients with chest pain admitted to the emergency room. The prevalence of acute myocardial infarction was 0·4.

Owing to this distribution of delay from the onset of pain to admission only the difference between the sensitivities of myoglobin and creatine kinase MB was statistically significant when all patients were included in the calculation of the sensitivity. Subgroup analysis of the sensitivities of myoglobin and creatine kinase in patients admitted during the 2–4 hour period (limits included), however, also showed a significantly ($p = 0·016$) higher sensitivity for myoglobin compared with creatine kinase (0·76 *v* 0·29). Table 3 shows the false positive diagnoses of acute myocardial infarction for creatine kinase, creatine kinase MB activity, or the immunoturbidimetric myoglobin assay. The specificity, positive predictive value, and likelihood ratio of myoglobin were significantly higher than for creatine kinase. The sensitivity and Youden index for myoglobin were significantly higher than for creatine kinase MB activity (table 2).

Fifteen patients with myocardial infarction presented with a non-diagnostic electrocardiogram to the emergency ward within six hours (median two hours) of the onset of chest pain. In these potential candidates for fibrinolytic therapy the sensitivity of myoglobin (0·6, 95% CI 0·35 to 0·85) was significantly higher than that of creatine kinase (0·33, 95% CI 0·09 to 0·57) and creatine kinase MB activity (0·13, 95% CI interval 0 to 0·3).

MYOGLOBIN, CREATINE KINASE, AND CREATINE KINASE MB ACTIVITY SENSITIVITIES BEFORE THE START OF THROMBOLYTIC THERAPY

Table 4 shows the sensitivities of myoglobin, creatine kinase, and creatine kinase MB activity during the early stages of acute myocardial infarction before the start of thrombolytic treatment. This table is based on the combined analysis of the data from emergency room patients and from the blood samples taken from patients with myocardial infarction in part 1 of our study at admission to the coronary care unit before thrombolytic treatment. Patients who had had cardiopulmonary resuscitation or defibrillation therapy were also excluded from data analysis. Myoglobin was significantly more sensitive than creatine kinase MB during the 0–6 hour period and significantly more sensitive than creatine kinase activity during the 2–4 hour period after the onset of chest pain. Almost all patients (92%) had increased plasma myoglobin concentrations during the 4–6 hour period.

Discussion

The immunoturbidimetric myoglobin assay allows fast and convenient myoglobin determinations of high analytical quality. Intra and inter assay coefficients of variation are within acceptable limits. Interference by rheumatoid factors, haemoglobin, bilirubin, and triglycerides was negligible under routine conditions. The correlation between immunoturbidimetric results and radioimmunoassay myoglobin results was good. The results of immunoturbidimetric myoglobin assay are available within 1–2 minutes of the start of the assay. These properties make this method

Table 2 Comparison of myoglobin, creatine kinase (CK) and creatine kinase MB activity in the emergency room diagnosis on admission of acute myocardial infarction in 126 patients with chest pain

	CK MB activity	*CK activity*	*Myoglobin*
Cut off value	10 U/l	70 U/l	70 µg/l
Sensitivity	0·32 (0 24 to 0·4)	0·44 (0·35 to 0·53)	0·45 (0·36 to 0·54)
Specificity	0·92 (0·87 to 0·97)	0·82 (0·75 to 0·89)	0·91 (0·86 to 0·96)
Positive predictive value	0·72 (0·53 to 0·91)	0·63 (0·53 to 0·71)	0·77 (0·70 to 0·84)
Negative predictive value	0·66 (0·58 to 0·74)	0·68 (0·6 to 0·76)	0·71 (0·63 to 0·79)
Efficiency	0·67 (0·59 to 0·75)	0·67 (0·59 to 0·75)	0·72 (0·64 to 0·80)
Youden index	0·24 (0·17 to 0·31)	0 26 (0·18 to 0·34)	0·36 (0·28 to 0·44)
Likelihood ratio	4 (1·6 to 6·4)	2·5 (1·8 to 3·2)	5 (2·6 to 7·4)

The prevalence of acute myocardial infarction was 0·4 (pretest odds 0·68). The delay of myocardial infarction patients from the onset of symptoms to admission ranged from 0·5 to 14·5 hours (median 2·25 hours). 95% confidence intervals are given in parentheses.

Table 3 Patients with false positive myoglobin, creatine kinase (CK), or creatine kinase MB test results

Patient	*Diagnosis*	*CK activity (cut off value 70 U/l)*	*CK MB activity (cut off value 10 U/l)*	*Myoglobin (cut off value 70 µg/l)*
1	Angina pectoris	87	13	65
2	Angina pectoris	201	4	<50
3	Musculoskeletal disorder	77	4	<50
4	Pulmonary embolism	108	8	<50
5	Angina pectoris	94	4	<50
6	DC countershock therapy	123	13	244
7	CK increase, unknown origin	138	4	<50
8	Angina pectoris	110	7	<50
9	Angina pectoris	170	7	54·2
10	Pericarditis	146	4	<50
11	Angina pectoris	97	4	<50
12	Pericarditis	114	4	62·8
13	Seizure	46	6	162
14	Angina pectoris	114	5	72·6
15	Angina pectoris	123	6	56·2
16	Gastritis	87	4	<50

ideally suited for the emergency room laboratory.

More extended and frequent blood sampling than in earlier studies confirmed previous reports[7-10] and showed statistically significant and clinically relevant differences in the time courses of myoglobin concentration and creatine kinase and creatine kinase MB activity after myocardial infarction and treatment with thrombolytic agents. The same patients were tested for myoglobin, creatine kinase, and creatine kinase MB, which cancelled out all possible biases that could have distorted the results (that is, delay between attack and treatment, different treatments, and size and site of infarction etc). Serial measurement of myoglobin in blood is a useful non-invasive means of monitoring the success of therapeutic recanalisation.[12 13] Reperfusion alters the release kinetics of myoglobin and other cardiac cytoplasmic proteins by washout from injured or dead myocytes.[18-20] A rapid increase and subsequent decrease in cardiac cytoplasmic proteins occur as perfusion is restored to the ischaemic regions of the heart. Ellis *et al* proposed a 4·6-fold increase in myoglobin during the first two hours after the initial attempt to restore perfusion in the infarct related vessel compared with myoglobin concentrations at the outset to discriminate between myocardial infarction patients with successful and failed reperfusion after thrombolytic therapy.[12] Rapid prediction of the outcome of therapeutic reperfusion by immunoturbidimetric myoglobin measurements could become increasingly important by allowing the use of alternative, invasive means of recanalisation if initial non-invasive attempts to restore reperfusion fail.

Table 4 A comparison of the sensitivity of myoglobin and creatine kinase (CK), and creatine kinase MB in the early stages of myocardial infarction (before thrombolytic treatment)

Delay between onset of symptoms and blood sampling	*Myoglobin*	*CK*	*CK MB activity*
≤2 h	0·23 (0·1 to 0·35)	0·13 (0·02 to 0·23)	0·05 (0·0 to 0·12)
>2 and ≤4 h	0·82 (0 69 to 0·95)	0·29 (0 14 to 0·44)	0·23 (0·08 to 0·38)
>4 and ≤ 6 h	0·92 (0·77 to 1·0)	0·75 (0·51 to 0·99)	0·33 (0·14 to 0·61)

Calculations of sensitivities are based on cut off values: 70 µg/l (myoglobin), 70 U/l (creatine kinase activity), and 10 U/l (creatine kinase MB activity). 95% confidence intervals are given in parentheses. Blood samples obtained from patients after cardiopulmonary resuscitation, defibrillation, or thrombolytic therapy were excluded from data analysis.

Acute myocardial infarctions, however, must be diagnosed and confirmed before the start of thrombolytic therapy. Therefore, we tested the sensitivity of myoglobin, creatine kinase, and creatine kinase MB in blood samples obtained before thrombolytic therapy. Neither myoglobin nor creatine kinase and creatine kinase MB were clinically efficient for diagnosing myocardial infarction within the first two hours after the onset of chest pain (0·23 *v* 0·13 and 0·05). Myoglobin was significantly more sensitive than creatine kinase MB activity during the 0–6 hour period and significantly more sensitive than creatine kinase activity during the 2–4 hour period after the onset of chest pain (0·82 *v* 0·29). Myoglobin was increased in almost all patients who were admitted between the fourth and sixth hour after the onset of symptoms. The difference between the sensitivities of myoglobin and creatine kinase (0·92 *v* 0·75) were not statistically significant probably because few patients (n = 12) were admitted during this interval. Myoglobin was significantly more sensitive in patients with myocardial infarction who presented with a non-diagnostic electrocardiogram on admission. This result accords with a recent report in which myoglobin was shown to be a strong independent predictor of myocardial infarction in patients with symptoms of short duration and to provide additional diagnostic information in patients without ST elevation.[27]

As a test to confirm the diagnosis of myocardial infarction myoglobin has two limitations. First, myoglobin shows earlier peak and return to normal values than creatine kinase and creatine kinase MB after myocardial infarction. Myoglobin must be measured soon after a heart attack. If hospital admission is delayed for 12–24 hours or more myoglobin concentrations will have fallen sharply and may be within the reference range again. Thus if chest pain is recurrent the myoglobin concentration may be a better indicator of further tissue necrosis than creatine kinase and creatine kinase MB. Second, myoglobin lacks specificity for cardiac muscle. When the test result is positive the clinical setting must be taken into account. In the absence of concomitant damage to skeletal muscle or severely impaired renal function a positive myoglobin test result predicts myocardial infarction with a very high probability. The specificities of myoglobin and creatine kinase activity in patients with chest pain were surprisingly high because we studied patients in the emergency room after injured patients had preselected for treatment elsewhere. The specificity of myoglobin and creatine kinase activity in the detection of myocardial infarction will be lower in a population that includes cases of acute or chronic skeletal muscle damage caused by injury, burns, surgery, etc. A negative myoglobin assay result in the 4–12 h period after the onset of the infarct related symptoms on the other hand allows acute myocardial infarction to be ruled out within a few minutes with a very high probability.

Finally, immunoturbidimetric myoglobin measurments do contribute to the diagnosis of acute myocardial infarction in the subgroup of infarct patients presenting early with non-diagnostic electrocardiograms.

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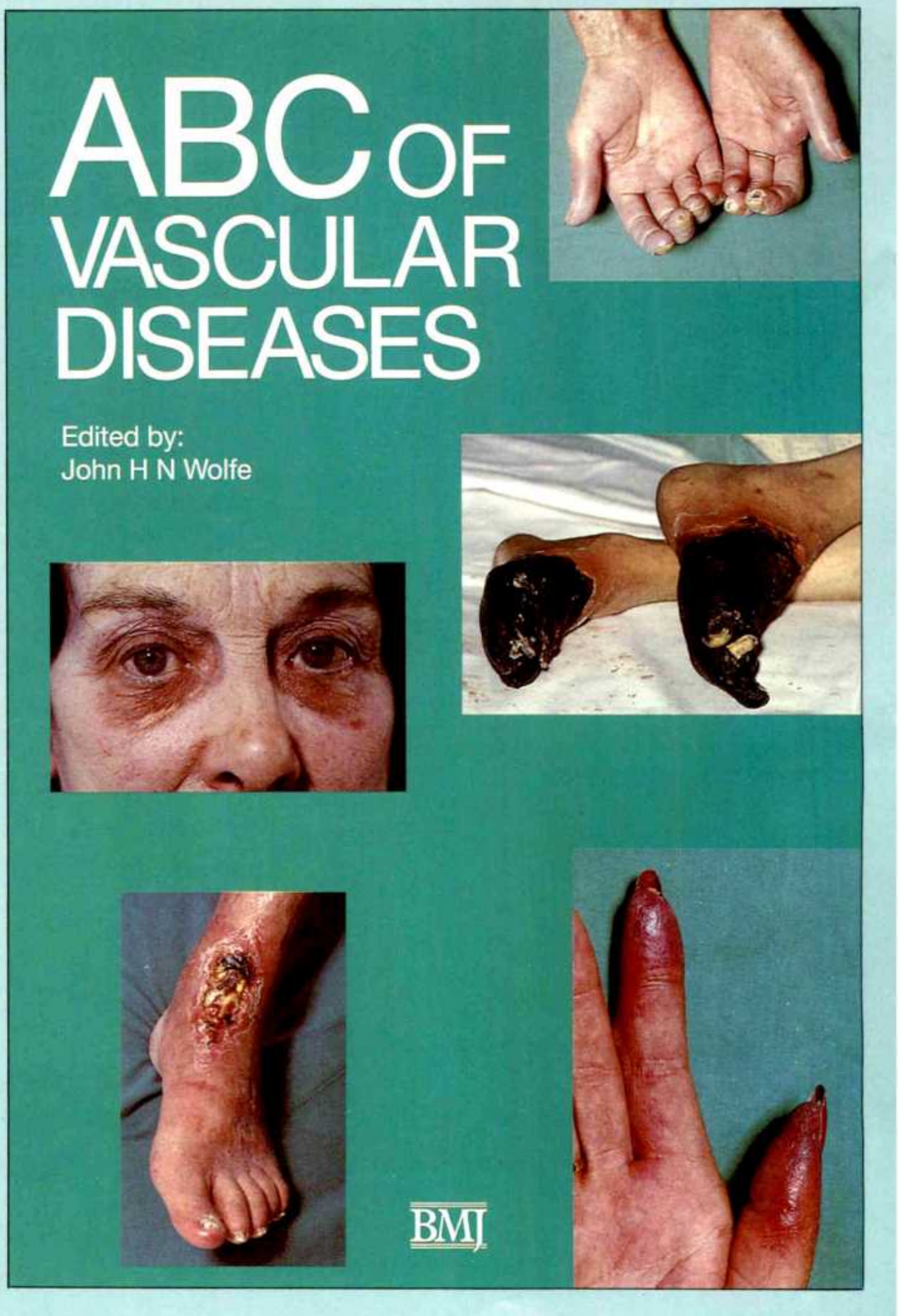

Br Heart J 1992;55:469–72

Short-stepping gait in severe heart failure

S W Davies, C A Greig, S L Jordan, D W Grieve, D P Lipkin

Abstract

***Background*—Patients with severe chronic heart failure seem to take shorter steps than healthy controls when walking on a treadmill and when walking freely along a corridor. In healthy individuals the pattern of walking affects the oxygen cost of exercise, and so this observation might be relevant to the limitation of exercise in heart failure.**

***Method*—Length of stride was analysed as stride/stature index in 15 controls, 10 patients with moderate heart failure, 10 patients with severe heart failure, and 10 patients with angina, walking at a constant speed/stature index.**

***Results*—The stride/stature index was 0·64 in the controls in patients with New York Heart Association (NYHA) class II heart failure, and in patients with angina. It was 0·49 in patients with NYHA class III heart failure. In the patients with heart failure the stride/stature index correlated with exercise capacity determined as peak oxygen consumption $\dot{V}O_2max$ ($R = +0·62$, $p < 0·005$). When healthy controls walked in time to a metronome adjusted to decrease their stride/stature index to approximately that seen in severe heart failure steady-state oxygen consumption increased by a mean of 15%.**

***Conclusions*—The length of stride is reduced in severe heart failure, and when healthy controls adopt this gait the oxygen cost of walking is increased. A short-stepping gait may contribute to the limitation of exercise capacity in heart failure.**

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A major symptom of patients with chronic heart failure is the limitation of exercise capacity by dyspnoea or by fatigue.[1 2] Physiological studies of healthy individuals in the 1950s showed that the pattern of walking influenced the oxygen cost of walking a given distance.[3-5] Preliminary observations when patients with chronic heart failure were exercise tested suggested that they took shorter and more frequent steps than normal, which in extreme cases amounted to a shuffling gait. These observations were confirmed when the same patients walked freely along a corridor.

It is possible that a short-stepping gait in chronic heart failure influences oxygen consumption and thus exercise capacity. We performed a simple quantitative analysis of gait in patients with chronic heart failure and in controls to determine the prevalence of abnormal gait and its importance. We also studied the effects of artificially altering the pattern of walking in the controls.

Patients and methods

PATIENT SELECTION

Twenty patients (six women and 14 men) with chronic left heart failure who were in New York Heart Association categories II and III were recruited from outpatient clinics. The left ventricular ejection fraction determined by radionuclide gated blood pool scanning was <45% in all patients. The aetiology of heart failure in each patient was ischaemic heart disease, and patients had been clinically stable for at least three months before the study. It was our intention to study a group of patients with *stable* chronic heart failure, without current angina, pulmonary disease, or other symptoms and conditions that might interfere with their ability to walk normally on the treadmill. Therefore the exclusion criteria were: (*a*) a history of recent angina or abnormal ST segment changes or both during exertion; (*b*) significant valve disease diagnosed by history, clinical examination, chest *x* ray, electrocardiogram, and echocardiogram; (*c*) primary lung disease as judged by history, clinical examination, chest *x* ray, and standard lung function tests (that is forced expiratory volume in one second, forced vital capacity, or diffusing capacity for lung carbon monoxide, <70% of predicted normal values); (*d*) disturbance of balance or musculoskeletal problems that might affect treadmill exercise.

Ten patients with stable angina in New York Heart Association (NYHA) categories II and III were recruited from outpatient clinics. None had any evidence of left ventricular failure, and each had <1 mm ST segment depression at peak exertion.

Fifteen age matched controls were recruited from among members of the laboratory staff and healthy elderly subjects participating in a general practice survey of the elderly in the community. None had any evidence of cardiac or respiratory disease as judged by history, physical examination, and resting 12 lead electrocardiogram. Gait indices in healthy people over a range of different ages had already been established in this laboratory by Grieve[6] and were used for reference.

The project was approved by the local ethics committee, and all subjects gave written consent. Each subject was required to attend the hospital on at least three occasions for exercise testing and associated tests, and those who agreed to enter the study were thus self-selected for a high level of cooperation. Subjects were unaware of the purpose of the study.

FREE CORRIDOR WALKING

Subjects walked freely along a 250 m corridor, with the instruction to walk at their "usual comfortable pace". No data were recorded until subjects reached the 50 m mark, to allow them to settle into a rhythm and pace of walking; the time taken and the number of strides taken over the final 200 m were recorded.

TREADMILL EXERCISE TESTING

Subjects were practised in treadmill exercise, and performed maximal symptom-limited exercise according to the modified Bruce protocol. Collection of mixed expired gases allowed the determination of ventilation by argon dilution and of oxygen consumption.[7] Exercise capacity was taken as peak oxygen consumption (Vo_2max). The reproducibility of Vo_2max determined on repeat testing was within 10% (mean difference −0·19 $ml.kg^{-1}.min^{-1}$, standard deviation of the differences ±1·18 $ml.kg^{-1}.min^{-1}$).

ANALYSIS OF GAIT

We checked the speed of the treadmill belt while each subject was exercising by recording the time taken for marks on the belt of known length to pass the observer. Because stride length depends on speed and on height,[6] each subject was exercised at a speed adjusted for his or her height. Height was measured with a Harpenden stadiometer and subjects walked at a treadmill speed calculated to give a speed/stature ratio of 0·5 s^{-1} (approximately 2 mph (3 km/h) in most subjects). When a steady state was attained for oxygen consumption and number of strides per unit time, we recorded the number of strides per minute and from the known velocity of the treadmill belt we obtained the stride length. The stride/stature index was then calculated as stride length divided by height.[6] The reproducibility of stride/stature analysis on repeat testing was within 10% (mean difference +0·02, standard deviation of the differences ±0·04).

WALKING TO A METRONOME

On a separate occasion steady state oxygen consumption was determined for 12 controls walking under each of three different conditions. First, with the treadmill set to a speed/stature index of 0·5 s^{-1} subjects walked with their normal gait. Second, subjects were then asked to walk in time to a metronome set to a rate calculated to quicken their step and to give a stride/stature ratio similar to that seen in patients with heart failure (approximately 0·5). Third, the metronome was reset to their previously recorded natural stepping rate.

STATISTICAL ANALYSIS

Because normal distribution of the values can not be assumed we used non-parametric statistics throughout. Values are given as median and range, comparisons between groups were made by the Mann-Whitney U-Statistic, and paired comparisons were made by the Wilcoxon test. Correlations were explored by means of the Spearman rank correlation coefficient. The reproducibility of repeat testing was assessed by the algebraic mean difference and the standard deviation of the differences.

Results

PATIENT CHARACTERISTICS

Patients with chronic heart failure were aged 47–78 years (median 65) and the left ventricular ejection fraction was 5–40% (median 23%). Peak oxygen consumption Vo_2max was 11.9–23·4 $ml.kg^{-1}.min^{-1}$ (median 14·8 $ml.kg^{-1}.min^{-1}$). The controls were aged 50–75 years (median 66). Peak oxygen consumption Vo_2max was 33·9–55·7 $ml.kg^{-1}.min^{-1}$ (median 40·8 $ml.kg^{-1}.min^{-1}$). Patients with angina were aged 45–71 years (median 63). Peak oxygen consumption was not determined in this group.

GAIT ANALYSIS: FREE CORRIDOR WALKING

The free walking speed/stature index was similar in controls (0·57–0·84, median 0·70 s^{-1}) and in angina (0·59–0·82, median 0·70 s^{-1}). The speed/stature index for free walking was reduced in patients with NYHA class II heart failure (0·50–0·77, median 0·62 s^{-1}, $p < 0·005$ compared with controls) and in class III heart failure (0·42–0·60, median 0·50 s^{-1}, $p < 0·001$ compared with controls). The stride/stature index was similar in controls (0·71–0·96, median 0·82) and in patients with angina (0·64–0·98, median 0·81) but was reduced in patients with NYHA class II heart failure (0·61–0·89, median 0·74, $p < 0·05$ compared with controls) and in patients with class III heart failure (0·33–0·56, median 0·48, $p < 0·001$ compared with controls).

Figure 1 shows the stride/stature index plotted against the speed/stature index. Values for patients with class III heart failure lie below the normal range previously defined in this laboratory.[7]

GAIT ANALYSIS: STANDARDISED TREADMILL SPEED

At a constant speed/stature index of 0·5 s^{-1} the stride/stature index was not significantly different in controls (0·49–0·78, median 0·63),

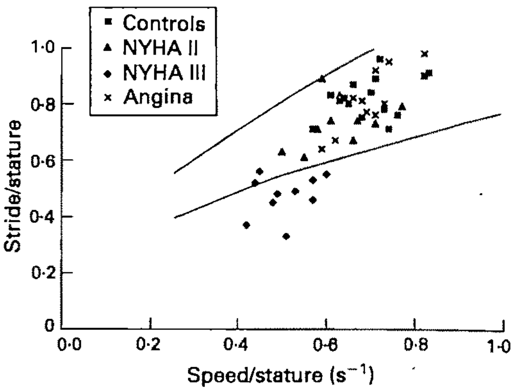

Figure 1 Normalised length of stride (stride/stature) and normalised speed (speed/stature) during free corridor walking. The two lines define the normal range, taken from Grieve 1989.[6]

in NYHA class II heart failure (0·57–0·81, median 0·65), and in patients with angina (0·55–0·71, median 0·64). The stride/stature index was reduced in NYHA class III heart failure (0·33–0·60, median 0·49) ($p < 0·001$ compared with each of the other groups) (fig 2).

Within the group of patients with heart failure (class II and class III) the stride/stature index correlated with Vo$_2$max, $R = +0·62$, $p < 0·005$ (fig 3).

ARTIFICIALLY SHORTENED STRIDE IN HEALTHY INDIVIDUALS

When 12 controls exercised at a constant speed/stature of 0·5 s^{-1} and then walked in time to metronome adjusted to give a stride length/stature index of approximately 0·5, the steady state oxygen consumption rose from 10·1–14·0 (median 11·7) ml.kg^{-1}.min^{-1} to 10·1–14·2 (median 13·0) ml.kg^{-1}.min^{-1}, $p < 0·005$ (fig 4). When subjects then walked in time to the metronome reset to their original stepping rate, the steady state oxygen consumption decreased to 10·5–13·8 (median 11·6) ml.kg^{-1}.min^{-1}. The mean increase in steady state oxygen consumption at the shortened stride/stature index was 15%.

Discussion

Limitation of exercise capacity by dyspnoea and by fatigue is a common symptom of patients with chronic heart failure[1,2] but the pathophysiological basis is unclear.[8,9] It has previously been noted that during treadmill exercise, patients with chronic heart failure take shorter and more frequent steps than controls. If this gait were inefficient it might contribute to the limitation of exercise.

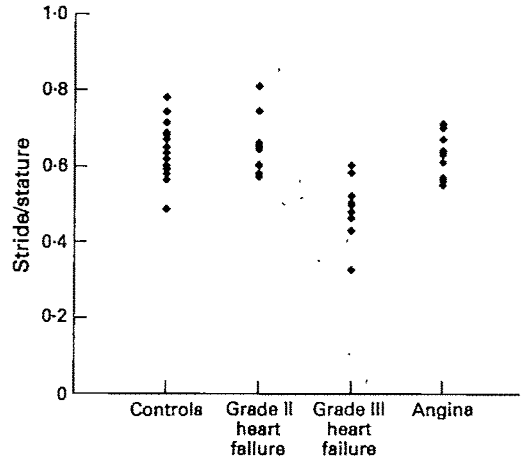

Figure 2 Standardised length of stride (stride/stature) at a standardised speed (speed/stature 0·5^{-1} s).

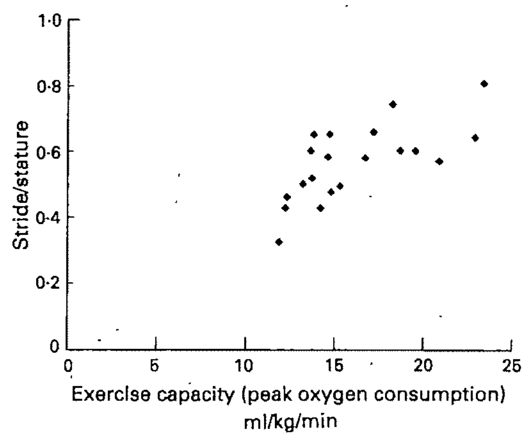

Figure 3 Relation between stride/stature and exercise capacity (Vo$_2$max) in heart failure.

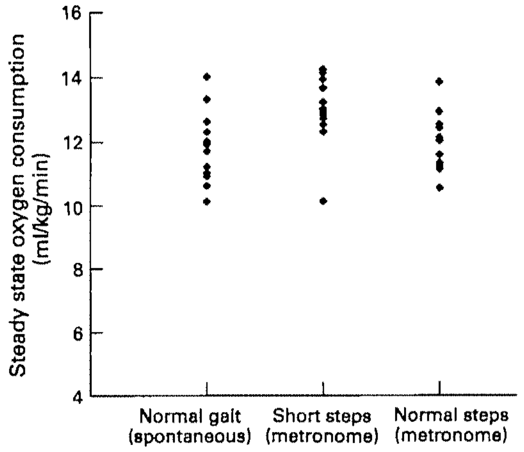

Figure 4 Steady state oxygen consumption in controls walking normally (unconstrained), constrained to a short stride/stature, and constrained to their normal stride/stature.

Analysis of the walking pattern in healthy people has defined ranges for simple indices of gait such as the stride length.[6,10,11] Stride length is usually standardised to the subject's height to give a "stride/stature index", and walking speed is similarly expressed as a "speed/stature index".[6,11] The stride/stature index depends on the age of the subject and on walking speed.[6,11,12] These relations are the same for women and for men when standardised for height.[6]

We measured the short-stepping gait of patients with severe chronic heart failure. Possible reasons for this gait may lie in the abnormalities of blood supply, histology, biochemistry, and strength of skeletal muscle in heart failure.[13–16] First, it is possible that the muscles are less able to sustain the contraction necessary for a long stride: walking speed and the number of steps taken correlate with calf muscle strength in normal elderly subjects.[17,18] Second, frequent short steps may minimise discomfort in the muscles: important reflexes may arise from the sensory endings in skeletal muscle,[19] and leg discomfort is associated with reduced walking speed in the elderly.[17,18] Third, a short-stepping gait might reflect anxiety in a person exercising on the treadmill. However, all subjects in the present study were well practised in treadmill exercise and were not overtly anxious; furthermore, the short-stepping gait was as apparent during free corridor walking as during treadmill exercise.

Theoretical considerations suggest that there should be an optimal speed and pattern of walking for which the mechanical power output is a minimum.[20] Actual observations have shown that oxygen consumption during walking varies with the speed and pattern of gait and that there is an optimal pattern of walking for which oxygen consumption is at a minimum (fig 5).[5,10,21]

Attempts to modify the stride length of patients with severe heart failure were unsuccessful because they were unable consistently to lengthen their stride to walk in time with a

Figure 5 Relation between speed of walking and oxygen consumption in a healthy individual (from Ralston 1958[5]). (Reproduced with permission of Springer-Verlag.)

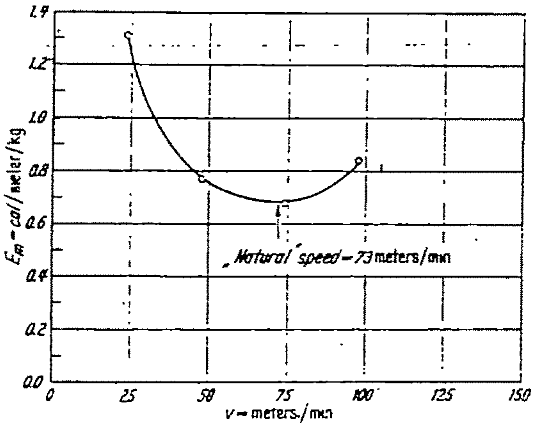

Fig. 3. Normal male subject. Relation between energy expenditure in cal/meter/kg and speed. Arrow indicates the "natural" walking speed of subject

preset metronome. However, we were able to measure the effects of shortening the relative stride of controls to values seen in patients with heart failure and this manoeuvre increased steady-state oxygen consumption by a mean of 15%. This change might simply have been the result of being constrained to walk in time to the metronome because precisely timed limb movements often involve the simultaneous activation of agonist and antagonist muscle groups. In the present study the change is attributable to the shortened stride rather than to the metronome because when the metronome was set back to the previously noted spontaneous stepping rate, steady state oxygen consumption returned to baseline values.

These observations raise the possibility that the short stepping gait of severe chronic heart failure is inefficient in terms of oxygen consumption. If this were so it might increase oxygen consumption during exercise at a given workload and contribute to the limitation of exercise capacity. If Vo_2max is severely limited, then even a small increase in the oxygen cost of a task may make the difference between being able to complete a task. This might then bear on the patient's ability to perform everyday activities, and thus on the quality of life.

We should however be cautious about inferring that the short-stepping gait in heart failure is suboptimal. In general, in adapting to disease the cardiorespiratory control systems adopt the most efficient pattern; for example, changes in ventilatory pattern in pulmonary and in cardiac disease.[22-24] It is therefore possible that the short-stepping gait represents the most efficient pattern of walking for patients with heart failure, represented by hypothetical line A in fig 6. Alternatively the short-stepping gait may be suboptimal in terms of oxygen consumption (hypothetical line B in fig 6) but represent the price paid for some other (unrecognised) advantage of this pattern of walking. It is unfortunate that we were unable to alter the gait of patients with severe heart failure.

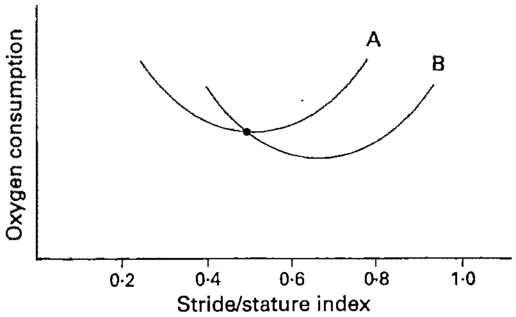

Figure 6 Possible relations between stride/stature and oxygen consumption in heart failure. Line A represents the theoretical possibility that the observed gait (indicated by the heavy dot) is the most efficient. Line B represents the possibility that the observed gait is suboptimal in terms of efficiency, requiring a higher oxygen consumption than a gait with a longer (normal) stride.

In summary, we found a short-stepping gait in chronic heart failure, that correlated with reduced exercise capacity (Vo_2 max). This may lead to an increased oxygen consumption at a given workload, and it is thus possible that an inefficient gait contributes to the limitation of exercise capacity in severe heart failure.

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Br Heart J 1992;68:473–7

Ventilation in chronic heart failure: effects of physical training

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Abstract

Objective—To assess the effects of exercise training on ventilatory function in chronic heart failure.

Design—Observer blinded random allocation crossover training and detraining trial.

Setting—Assessment in hospital based clinical laboratory; training home based.

Patients—22 patients with chronic heart failure (New York Heart Association (NYHA) class II or III) recruited from a tertiary referral centre. All finished the study.

Intervention—Bicycle ergometer exercise for 20 minutes a day, five days a week for eight weeks at 70%–80% of maximum heart rate.

Main outcome measures—Exercise capacity on graded incremental exercise test, minute ventilation, oxygen consumption and carbon dioxide output.

Results—Peak work load increased from 96 W to 112 W and peak oxygen consumption from 14·1 ml/kg/min to 15·4 ml/kg/min ($p < 0.01$). At submaximal workloads carbon dioxide excretion (V_{CO_2}) and minute ventilation (Vi) decreased significantly ($p < 0.05$) though oxygen consumption was unchanged. The relation between Vi and carbon dioxide excretion changed: the slope of the Vi to V_{CO_2} plot decreased from 38·6 to 35·3, indicating an improvement in overall ventilary efficiency. The instantaneous carbon dioxide ventilatory equivalent (Vi/V_{CO_2}) decreased at submaximal workloads, and reached a lower mimimum value after training, indicating that optimum ventilatory performance improved. The exercise capacity of patients was related to the optimum ventilatory performance. It is suggested that this may in part be mediated through changes in skeletal muscles.

Conclusion—Exercise training reduces the ventilatory abnormalities in chronic heart failure; thus some of these changes may be due to physical deconditioning.

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Reduced capacity to exercise in patients with chronic stable heart failure is often associated with breathlessness that may be defined as either a sense of laboured respiration or increased breathing frequency volume.[1 2] The origin of this symptom is multifactorial,[3] but increased ventilation plays a part. Haemodynamic abnormalities are only poorly correlated with the intensity of dyspnoea.[4] Other factors, such as the changes in skeletal muscles that cause the early start of acidosis during exercise[5] (as detected by magnetic resonance spectroscopy[6]) may increase ventilation during exercise and thus contribute to dyspnoea. Wasting, weakness, and early tiredness,[7] particularly of the leg muscles, increase the perception of the severity of exercise and through changes in respiratory reflexes may increase breathlessness. Drugs that reduce exercise dyspnoea in chronic heart failure often do so four to eight weeks after the acute haemodynamic improvement has occurred, and it may be that changes in some of the peripheral abnormalities of heart failure must take place first. We hypothesised that these abnormalities may be major limiting factors in their own right,[6] and that if the function of skeletal muscle were improved through a programme of physical training, increases in capacity to work and ventilatory function might follow.[8] We therefore evaluated the effect that a home based programme of physical training had on the ventilatory performance during exercise in patients with chronic stable heart failure.

Methods

The study was approved by the local ethics committee. Twenty two patients with chronic heart failure participated in the study (seven had participated in an earlier training study[8]). They were all men, mean age 64 (range 54–74) years. The aetiology was ischaemic heart disease in 19, dilated cardiomyopathy in two, and valvar disease in one. Thirteen patients were in New York Heart Association (NYHA) class II, and the rest were in class III. No patient had angina as a limiting symptom. Left ventricular ejection fraction by radionuclide ventriculography was mean (SD) 22 (8)%. All patients had been stable for at least three months before the study. Significant pulmonary disease was excluded clinically and by chest x ray films. All patients were taking diuretics, a mean frusemide equivalent dose of 84 (SD 21) mg. Nine were taking an angiotensin converting enzyme inhibitor.

Table 1 The effect of training on capacity to work and peak $\dot{V}O_2$ *(mean (SD))*

	Detrained	*Trained*	*p Value*	*Increase*
Exercise time (min)	14 3	16 3·4	0·001	14%
Total external work (kJ)	49 6 17·6	66·4 23·8	0·001	33%
Peak external work (W)	96 22	112 20	0·001	16%
Peak Vo_2 (ml/kg/min)	14·1 2·8	15·4 2·8	0·01	9%

STUDY DESIGN

Patients were entered in random order to a training or detraining period of a cross over study. After three baseline exercise tests, designed to ensure reproducibility and familiarity with the laboratory, patients were randomly assigned to either study period, with assessment at the end of each period. For training, patients were lent a Tunturi professional cycle ergometer for use five days each week for eight weeks. These cycle ergometers were used at home. Patients monitored their own heart rates during exercise with an electrocardiographically based pulse monitor (Micro Sports Lab Computer, Triad-colour, London). Patients warmed up with the resistance set at 25 W for one minute, and then increased the setting until the heart rate was 70%–80% of their previously determined maximum (thus automatically increasing the workload as training developed). After 20 minutes at this higher setting, patients cooled down for one minute at 25 W. Compliance was assessed by a revolution counter and expressed as a percentage of revolutions achieved divided by revolutions expected. In the detraining period, the exercise bicycle was removed, and the patient instructed to avoid all exercise that induced dyspnoea or fatigue. Resting left ventricular ejection fraction was measured by radionuclide ventriculography.

EXERCISE TESTS

Exercise capacity and respiratory performance were measured on a Tunturi bicycle ergometer in four minute 25 W incremental stages to exhaustion. Tests were performed at the same time of day, after an overnight fast, and before medication had been taken. Gas analysis[9 10] was performed by measuring inspired airflow (Harvard instruments dry gas meter for minute ventilation) and expiratory oxygen and carbon dioxide concentration by gas meter (570A and PA404, Servomex, Crowborough, Sussex). The instruments were calibrated against gas mixtures of known concentration at the start of each exercise test. Data from the dry gas meter and the gas analysers were transmitted on line to a Hewlett-Packard personal computer and converted, with standard formulas, to gas volumes at standard temperature and pressure. Breathing frequency was measured for the first 12 patients in the programme with a thermistor positioned proximally in the expiratory air pipe. Heart rate was recorded from the electrocardiograph and blood pressure was measured by a sphygmomanometer at the end of each four minute stage and at peak exercise.

STATISTICS

Patients were assessed by observers who were blind to their training state. Data were expressed as mean (SD). Results were compared before and after training with the paired Student's *t* test. The slope of minute ventilation to minute carbon dioxide excretion was found with a least squares fitting algorithm. Significance was accepted at the 5% level. Figures have standard error bars.

Results

The effects of training on exercise performance of seven of these 22 patients has previously been reported.[8] Baseline test did not differ from those obtained after detraining, and no carry over effects were detected. Training (table 1) produced a significant improvement in exercise capacity. At matched submaximal work loads there was no significant change in oxygen consumption (table 2), but the overall oxygen consumption for the exercise test compared with the total amount of external work performed fell from 0·243 (0·051) ml oxygen per Joule external work to 0·221 (0·043) ml oxygen per Joule external work ($p < 0·05$).

VENTILATORY PERFORMANCE

Minute ventilation showed highly significant decreases at submaximal workloads, but no change at peak exercise (table 3). An inverse correlation between peak minute ventilation and severity of heart failure has been reported in severe chronic heart failure,[11] but we found no such correlation within the group. There was a non-significant trend for the tidal volume to increase earlier and to a greater extent during exercise, with severity of disease.

GAS EXCHANGE

Carbon dioxide excretion decreased significantly at 50, 75, and 125 W submaximal workloads (table 2) and tended to decrease at other workloads. At peak exercise there was a significant increase in minute carbon dioxide excretion, with no significant change in minute ventilation. Carbon dioxide excretion is highly

Table 2 The effect of training on submaximal and peak oxygen consumption and carbon dioxide excretion. Data is in ml/kg/min (mean (SD))

Load	Vo_2 *Detrained*	Vo_2 *Trained*	*p Value*	Vco_2 *Detrained*	Vco_2 *Trained*	*p Value*
Rest	3·47 0·8	3·4 0·5	NS	3 0·5	2·9 0·6	NS
25W	6·08 1·1	6·13 0·8	NS	5·2 0·9	4·9 0·8	NS
50W	8·98 1·5	8·71 1·3	NS	8 1·4	7·3 1·1	0·02
75W	11·5 2·1	11·2 1·5	NS	11·3 1·9	10·4 1·5	0 03
100W	14·0 2·3	14·4 2·3	NS	14·8 1·9	14·4 2·4	NS
125W	15·7 3·2	15 6 2·4	NS	16·2 2·9	13·4 2·7	0 01
Peak	14·1 2 8	15·4 2·8	0·01	14·9 2·8	16·3 3·3	0 01

Table 3 Ventilation at matched submaximal and peak workloads (l/min)

Load	*Detrained*	*Trained*	*p Value*	*n*
Rest	11·3 2	10·5 1·9	0·05	22
25W	16·5 3·9	15 2	0·05	22
50W	23·4 6·8	20·9 4·7	0 005	22
75W	32·1 7	28·6 6·2	0·005	21
100W	41·8 8·9	38·1 7·6	0·05	14
125W	41 6·1	38·8 8·6	NS	5
Peak	47 8 9·2	48 5 9·6	NS	22

dependent on effective minute alveolar ventilation, and so to assess whether the changes in minute carbon dioxide excretion were related to the changes in minute ventilation, we plotted the change in minute carbon dioxide excretion that training induced against the reduction in minute ventilation at each minute of each workload for each patient and found that for all subjects there was a highly significant correlation (mean correlation $r = 0·88$ (0·11) ($p < 0·01$).

The time taken to reach a respiratory quotient (RQ = Vco_2/Vo_2) of unity increased significantly with training from 10·9 (2·9) minutes to 13·7 (2·8) minutes, $p < 0·01$, reflecting a delay in the start of anaerobic metabolism. At submaximal workloads, although not at rest or at peak workloads, the respiratory quotient was reduced significantly (fig 1).

The relation between minute ventilation and minute carbon dioxide excretion, which has been reported to be steeper in those with heart failure[11] was studied. In each patient the correlation between Vi and carbon dioxide excretion, found by simple regression analysis, exceeded 0·9. The slope of the Vi-Vco_2 line decreased from 38·6 (11·0) to 35·5 (8·4), $p < 0·01$ (ml of ventilation/ml. of carbon dioxide excretion). There was a significant inverse relation between the steepness of the Vi-Vco_2 slope and the capacity to exercise (detrained $r = 0·64$, $p < 0·001$, trained $r = 0·56$, $p < 0·01$), as previously described.[3]

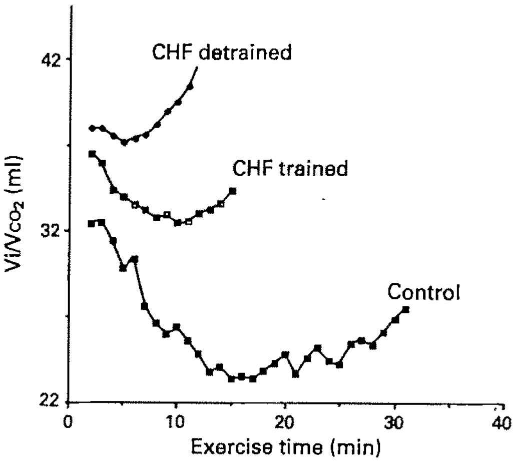

Figure 2 Carbon dioxide ventilatory equivalent (Vi/Vco_2) plotted against exercise time for one patient before and after training (CHF detrained, CHF trained). The normal control in this case was a healthy untrained 45 year old man.

Whereas the relation between minute ventilation and carbon dioxide production is linear, the relation between the ventilatory carbon dioxide equivalent (minute ventilation/carbon dioxide excretion) and exercise time is not. Each patient showed the same general pattern (fig 2). At rest the Vi/Vco_2 value was comparatively high. As exercise progressed the Vi/Vco_2 value progressively decreased until a trough point was reached. This point was established by taking the minimum numerical value of Vi/Vco_2. If there were more than two points with an identical minimum value, the middle one of the range was taken. With increasingly heavy workloads the carbon dioxide ventilatory equivalent increased, continuing to do so until exercise stopped. The trough point, which may be regarded as that part of the exercise test where patients require the least minute ventilation per unit of carbon dioxide excretion, was reached before training at 65·8 (13·5)% of peak work load, and after training at 69·6 (13)% of peak work load (NS). This point of maximum ventilatory efficiency with respect to carbon dioxide excretion correlated well with total exercise time before and after training (fig 3). The start and trough point were both affected by the training process (fig 4), both being lowered, and the time taken to reach the trough point was significantly delayed by training, from 7·9 (3) minutes to 10·1 (3·3) minutes. The steeper increase in minute ventilation at higher workloads (comparing the difference between the trough with maximum Vi/Vco_2), unlike the linear

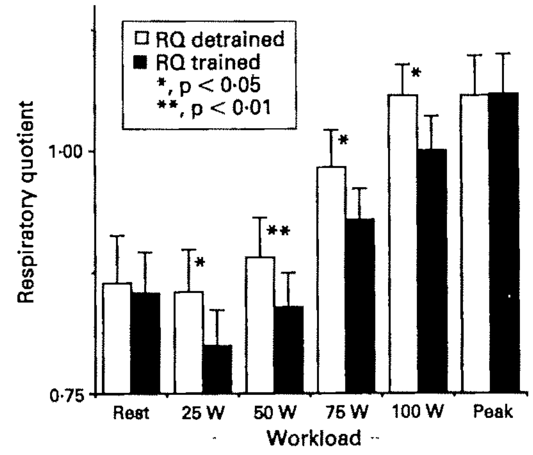

Figure 1 Effect of training on respiratory quotient: rest, matched submaximal and peak workloads.

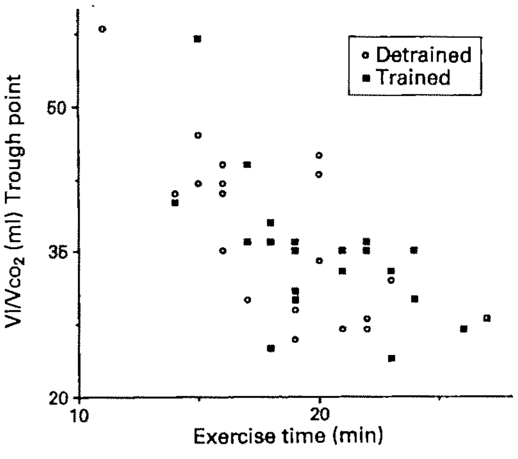

Figure 3 Relation between minimum point in the Vi/Vco_2 curve and capacity to exercise.

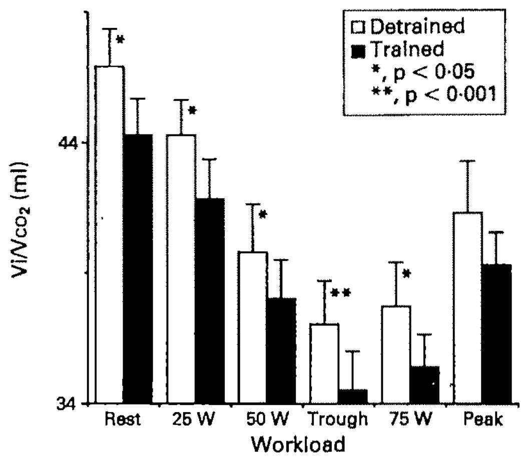

Figure 4 Effect of exercise and training on carbon dioxide ventilatory equivalent (Vi/Vco$_2$).

increase in minute ventilation at lower workloads, did not correlate with any measure of functional capacity.

Discussion

Short periods of physical training increase exercise capacity in patients with chronic heart failure.[8 12–16] With a modest home based programme of physical exercise our subjects showed an increase in capacity to work. Peak oxygen consumption, however, underestimates the degree of symptomatic improvement as much benefit is in the improved capacity to endure submaximal work. Our results show a 33% increase in total external work performed, with only a rather more modest 9% increase in peak oxygen consumption. More intensive training programs can increase submaximum (2/3 of peak) workload endurance by up to 52%.[13]

The mechanism of the increased work capacity may lie partially in the incomplete reversal of depressed peak cardiac output and raised peripheral resistance of chronic heart failure patients.[17 18] Training may increase blood supply to the leg, and partly reverse some of the skeletal muscle changes caused by chronic heart failure[6 19–21] by, for example, increasing energy producing enzymes, particularly fatty acid oxidative enzymes, and switching to a more efficient type of fibre distribution. An increase in the fatty acid contribution to energy production will lessen the respiratory quotient (Vco$_2$/Vo$_2$), and greater delivery and extraction of oxygen in the legs will delay anaerobic glycolysis.

Decreased carbon dioxide production and a later start of acidosis will both decrease submaximal minute ventilation. We have shown that a very close relation exists between the reductions in minute ventilation and in carbon dioxide excretion that training induces. This relation in itself does not necessarily imply causality due to the speed with which alveolar capillary carbon dioxide equilibrates with alveolar gas but as the carbon dioxide buffering capacity of the body is small compared with the carbon dioxide flux, and respiratory acidosis does not occur (indeed, in chronic heart failure there is a tendency to arterial hypocapnia and alkalosis[12]), this suggests that the reduction in minute ventilation is mainly metabolically mediated.

The 8·5% reduction in the slope of the Vi to Vco$_2$ relation, however, which is raised in heart failure[3 11] suggests that ventilation is decreased over and above the reduction in carbon dioxide production that is ventilatory efficiency is increased. This may be due to a reduction in pulmonary dead space, either due to an increase in tidal volume (though this is small), or to improved pulmonary haemodynamics. Overall pulmonary haemodynamics have not been found to change in previous training studies, though this does not preclude beneficial changes in the local balance between perfusion and ventilation. Alternatively, changes in the control of ventilation (possibly through changes in chemo and mechanoreceptors in the legs), may have contributed to the reduction in ventilation.

The relation between carbon dioxide excretion and minute ventilation was looked at in more detail, with the carbon dioxide ventilatory equivalent (Vi/Vco$_2$) plotted against workload. This curve gives the minute ventilation at any workload once it has been standardised for carbon dioxide production and so it represents ventilatory efficiency. In normal subjects, however, this is also correlated with chemoreceptor responsiveness to hypoxia and hypercapnia.[22] The point of maximum ventilatory efficiency was improved and delayed by the training process. The good correlation of this point with total exercise time suggests that optimum ventilatory performance is related in a meaningful way to capacity exercise in heart failure. The relation may be through pulmonary and systemic haemodynamics, chemoreceptor sensitivity, or skeletal muscle changes. This point of optimum ventilatory efficiency may be an objective method of assessing the efficacy of therapeutic interventions in the treatment of chronic heart failure.

It is often assumed that the Vi/Vco$_2$ relation is close to linear, so that the slope of the line can describe its behaviour. Although the individual correlation coefficients of Vi *v* Vco$_2$ are high ($>0·9$) this does not imply a straight line relation between the two. Figure 2 shows the relation is clearly not linear but turns up at the end so that we believe the plot of instantaneous Vi/Vco$_2$ *v* exercise time or load with its trough point gives more information than the conventional plot of Vi *v* Vco$_2$. This is supported by the better correlation between trough point Vi/Vco$_2$ and exercise time than between mean Vi/Vco$_2$ slope and exercise time.

In conclusion, we found that a short course of mild home based exercise training was effective in improving the exercise peformance of patients with NYHA class II and III stable chronic heart failure, improving peak exercise capacity, decreasing submaximal minute ventilation and carbon dioxide output, and improving ventilatory efficiency. It may be that some of these changes in chronic heart failure are the result of deconditioning rather than the heart failure itself.

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Br Heart J 1992;68:478–80

Management of the cardiovascular manifestations of poisoning by the Indian red scorpion (*Mesobuthus tamulus*)

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Abstract

***Objective*—The efficacy of nifedipine and prazosin in combination or alone in the management of cardiovascular manifestations caused to *Mesobuthus tamulus* poisoning was investigated.**

***Design*—Observation and study.**

***Setting*—Hospital at Mahad, Maharashtra, India.**

***Subjects*—62 patients who had been stung by a red scorpion were admitted from January to December 1990: 18 with hypertension, 15 with supraventricular tachycardia, 11 with pulmonary oedema, and 18 with local pain at the site of sting but no systemic involvement. Two patients with massive life-threatening pulmonary oedema were given intravenous sodium nitroprusside.**

***Results*—The combination of nifedipine and prazosin was more successful in preventing myocardial damage in 16 patients with hypertension than was nifedipine alone in two other patients with hypertension. Prazosin alone helped to alleviate the cardiovascular manifestations in eight patients with pulmonary oedema and 15 with supraventricular tachycardia. One patient with pulmonary oedema died and two recovered after they were given intravenous sodium nitroprusside.**

***Conclusion*—Nifedipine alone did not prevent myocardial damage unless the peripheral action of venom was blocked by prazosin.**

(*Br Heart J* 1992;68:478–80)

Mortality from *Mesobuthus* (formerly *Buthus* or *Buthotus*) *tamulus* stings in the Mahad region was about 30%.[1-5] We have studied this acute medical emergency since 1976. Our clinical observations and knowledge of the pathophysiology of scorpion stings in humans and dogs led to the use of vasodilators and calcium channel blockers which reduced mortality to 2–3%.[4,6-10]

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Patients and methods

Sixty two patients stung by red scorpions (*Mesobuthus tamulus*) were admitted to our hospital. Soon after being stung 44 patients had vomiting, profuse sweating, hypersalivation, priapism, and mild local pain at the site of the sting that were suggestive of autonomic storm. The other 18 had excruciating pain at the site of the sting that radiated to the adjacent dermatomes but no other signs or symptoms of systemic involvement. Local pain was treated by injecting 0·1–0·2 ml dehydroemetine (0·03%) at the site of the sting. Radiation of pain usually prevents patients from identifying the site, but the sting causes local sweating and a punctate haemorrhagic spot in subcutaneous tissue or skin resulting from rupture of the capillaries by the sharp sting. The 44 patients with systemic involvement were admitted and the following were closely monitored: heart rate, blood pressure, persistence of parasternal systolic lift, systolic murmur, gallops, rales, priapism, the appearance of the skin, and the temperature of the extremities. They were divided into three groups with different major clinical features: (*a*) hypertension; (*b*) tachycardia; and (*c*) pulmonary oedema.

HYPERTENSION

Eighteen patients had hypertension, loud protodiastolic gallop, a transient apical 2/6 systolic murmur of papillary muscle dysfunction, and systolic parasternal lift. They seemed frightened and had prominent eyes and a puffy face. The children were confused and agitated and looked lethargic. In two patients in this group pulmonary oedema subsequently developed.

TACHYCARDIA

Supraventricular atrial tachycardia (130–180 beats/min) with fast, thready peripheral pulsations and cold extremities developed in 15 children, 5–7 hours after they were stung. There was an improvement in clinical signs with an increase in tissue perfusion within 6–8 hours of treatment with oral prazosin alone (table). Hypovolaemia was corrected by oral rehydration solution. Agitated, confused and non-cooperative patients were given a 5% dextrose saline drip.

PULMONARY OEDEMA

Eleven patients had acute pulmonary oedema, tachycardia, cold extremities, ashen grey conjuctivae, tongue, and lips and fingers and toes that looked frostbitten because of severe vasoconstriction. Such patients usually presented later (table) than the other two groups. Two

Clinical manifestations

Data	*Hypertension*	*Tachycardia*	*Pulmonary oedema*
Number of patients	18 (11 M: 7 F)	15 (8 M: 7 F)	11 (6 M: 5 F)
Age (yr)	2–72 (39)	1·9–11 (9)	9·50 (22)
Interval between sting and admission to hospital (h)	1·5–65 (3)	1–24 (5·7)	2–52 (11·6)
Blood pressure (mm Hg)	130/90–220/140	60/90–110/90	90/70 unrecordable (PCF)
Heart rate (beats/min)	54–150 (87)	130–180 (154)	83–150 (125)
Interval between treatment and the start of clinical improvement (h)	4–20 (13·6)	6–18 (12)	10–24 (16)

Mean is given in parentheses. PCF, peripheral circulatory failure.

of these patients (aged 10 and 25 years) sought help 12 and 4·5 hours after being stung. They had life-threatening massive pulmonary oedema and were cyanosed and coughing up pinkish froth through their mouths and nostrils. The electrocardiographic findings are shown in the figure.

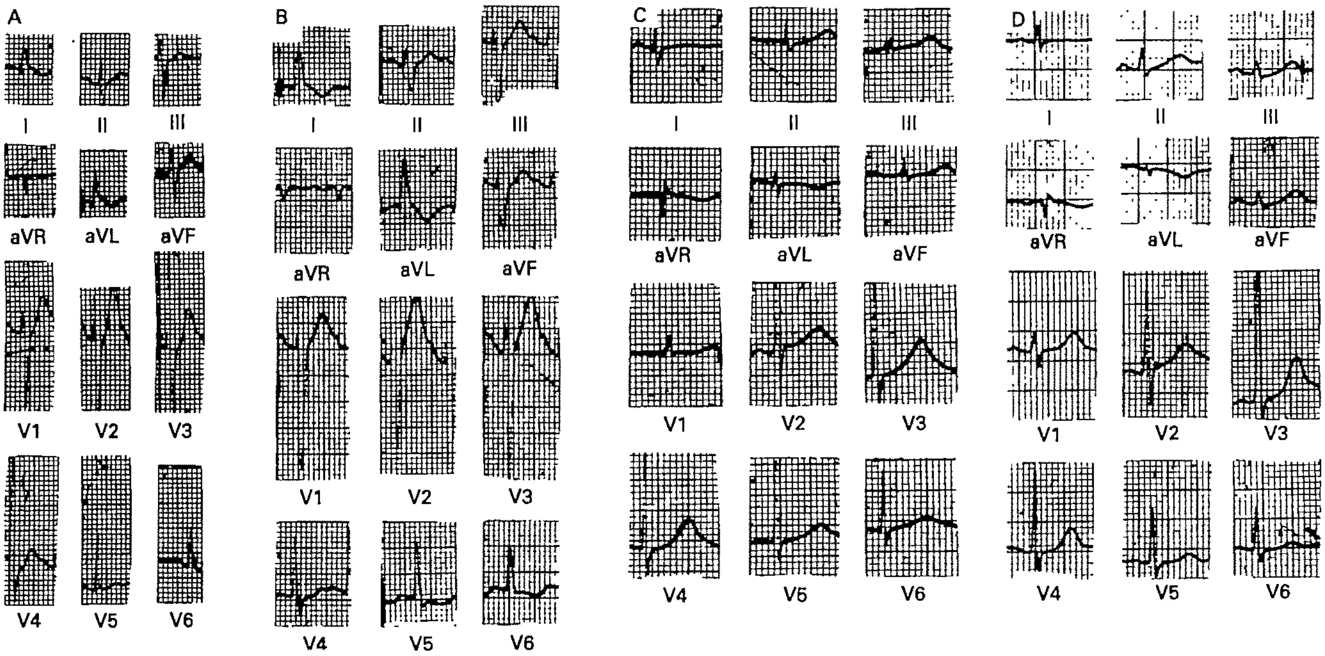
A 25 year old man, who was brought in three days after the sting, had right-sided hemiplegia preceded by pulmonary oedema. A 2 year old girl became unconscious 14 hours after the sting. She had generalised convulsions, pin-point pupils that reacted poorly to light, undetectable peripheral pulses and blood pressure, and moist rales. The electrocardiogram showed a heart rate of 215 beats/min, a left anterior hemiblock, a low voltage pattern, and ST segment depression of 5 mm in leads V2, V3, and V4.

Sixteen patients with hypertension on admission were given a single dose of 5 mg sublingual nifedipine and oral prazosin (250 μg to children and 500 μg to adults). Prazosin was repeated six hourly until the extremities were cold (table). The blood pressure in the remaining two patients with hypertension was controlled with sublingual nifedipine alone; the dose was repeated to control rebound hypertension. Three hours later despite control of arterial pressure pulmonary oedema developed in these two patients who recovered after additional treatment with oral prazosin. Patients with tachycardia were treated with prazosin alone and hydration therapy. Those with pulmonary oedema were propped up and given intravenous aminophylline, sodium bicarbonate, oral prazosin, and oxygen by mask. Two of these patients had life-threatening massive pulmonary oedema. They were treated with an intravenous sodium nitroprusside drip. The patient who died had severe pulmonary oedema, tachycardia, convulsions, pin-point poorly reacting pupils, and peripheral circulatory failure. He was treated with intravenous chlorpromazine, aminophylline, sodium bicarbonate, fursemide (to reduce the preload), oxygen by mask, and a 5% dextrose infusion, but he died of a cardiac arrest.

Discussion

This was an observational study rather than a strict scientific trial. Because mortality is so high in patients with cardiological symptoms and treatment reduced it to 1·6% we believe that it would be unethical to withold treatment.

Scorpion stings occur in tropical and subtropical regions and are common in rural India.[11–15] The haemodynamic and myocardial effects of scorpion venom have been reported



Electrocardiograms from a 10 year old boy who presented with pulmonary oedema 12 hours after a scorpion sting. (A) On admission there was left axis deviation and ST segment elevation and T inversion in leads I and aVL. (B) Twelve hours after admission there was left bundle branch block with left axis deviation and associated T inversion in leads I, aVL, and V5–V6. (C) On day 11 there was there was regression of acute changes. Note right axis deviation and tall R waves in right precordial leads, with T inversion in aVL (QT 0·48 s). (D) After five weeks the electrocardiograms were essentially similar to C.

in experimental animals as well as in humans.[10 16–18] The red scorpion (*Mesobuthus tamulus*) was responsible for the stings reported here. Its venom is a potent stimulator of the autonomic nervous system causing a sudden outpouring of endogenous catecholamines into the circulation.[19 20] The venom initially causes transient cholinergic stimulation (vomiting, profuse sweating, bradycardia, priapism, hypersalivation, and hypotension) which is followed by sustained adrenergic hyperactivity (hypertension, tachycardia, and myocardial failure). The adrenergic phase but not the cholinergic phase is a dose dependent phenomenon.[21 22] On the basis of clinical manifestations and known pathophysiology of scorpion envenomation we devised an approach to management that did not use antivenin. We treated patients in our facility with what was available to us. We believe that transporting these patients to the nearest big hospital can contribute to their death.[4] Nifedipine, a calcium channel blocker, is useful for the immediate treatment of hypertension and helps to reduce the myocardial contractility enhanced by autonomic stimulation.[8 23] In addition nifedipine may protect the heart muscle from the toxic effects of scorpion venom.[24] Experimental studies showed that myocardial damage after a scorpion envenomation is caused by an influx of calcium ions into the heart muscle cells.[25] Sudden rebound of hypertension in some patients can be explained by recurrent envenoming. Prazosin, a post synaptic α blocker, is known to reduce preload and left ventricular impedance. Its hypotensive action may also be due to inhibition of adrenaline synthesis at the betahydroxylation step.[26] Thus prazosin blocks the action of adrenaline.[27 28] Plasma renin activity was not significantly increased in response to blood pressure lowering action of prazosin.[26] Nifedipine alone does not prevent myocardial damage unless the peripheral action of venom is blocked by the sympathetic α-blocker, prazosin.[29] Although blood pressure was controlled by nifedipine, subsequent myocardial failure responded only after the addition of oral prazosin. Most of the electrocardiographic abnormalities in human scorpion sting, including ST-T changes, closely resemble the electrocardiograms in patients with congenital QT interval syndrome.[30] The outpouring of catecholamines in response to the scorpion sting is probably a major factor in the pathogenesis of ST-T changes.[31] The possibility of a direct effect of the toxin on the myocardium, however, cannot be excluded.[32]

In dogs various metabolic disturbances caused by scorpion venom were reversed by the specific scorpion antivenin essentially through the release of insulin.[33] Prazosin inhibits the suppression of insulin secretion caused by scorpion envenoming.[34] As a consequence of this action it helps to reverse the metabolic changes and arrest myocardial damage caused by liberated free fatty acids and phospholipids.[7] We have found that the combination of nifedipine and prazosin is a pharmacological antidote to the action of venom. This treatment is quick acting, easily available, relatively cheap and does not risk anaphylaxis.[35]

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Use of casts in the necropsy diagnosis of fetal congenital heart disease

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Abstract

***Objective*—To evaluate a casting technique in the interpretation of fetal cardiac anatomy.**

***Design*—In 32 fetuses, the echocardiographic and cast features were compared and correlated.**

***Patients*—Three normal fetal heart specimens from spontaneous abortuses and 32 specimens from spontaneous or induced abortions with congenital heart malformation.**

***Results*—There was close correlation between the echocardiographic and anatomical features in 32 abnormal fetuses studied. In some, additional features of diagnosis could be displayed on the cast and the relative sizes of the cardiac structures could be appreciated and defined.**

***Conclusions*—With increasing echocardiographic detection of congenital heart disease in early prenatal life, an increasing number of fetal heart specimens of small size are dissected for pathological confirmation. The use of silicone rubber casts to reproduce the internal anatomy proved a useful addition to dissection, providing a three dimensional model of the cardiac defect.**

(*Br Heart J* 1992;68:481–4)

Fetal echocardiography has become established as a reliable technique for the evaluation of the normal and abnormal fetal heart.[1-3] Echocardiographic and anatomical correlation has formed an important part of the learning experience in this new field.[3 4] The formation of casts of the cardiovascular system has been described since the 16th century. Leonardo da Vinci referred to the use of wax for casting the cavity of a bull's heart in his notebooks and a number of other materials have been used. Thompsett achieved very accurate representation of the cardiac chambers by using resins and then dissolving the surrounding tissues in acid.[5] As this involves destruction of the anatomical specimen, the technique has not been generally applied to clinical practice. More recently, silastic polymers mixed with

Data on cases

Case	*Echocardiographic diagnosis*	*Gestation (weeks)*	*Additional cast finding*
1	Distal arch hypoplasia	20	Extent of hypoplasia defined
2	HLHS, arch hypoplasia	20	1·5 mm VSD
3	Critical AS	19	Coarctation
4	Critical AS	20	Arch hypoplasia, bicuspid AoV
5	Critical AS	23	Unicuspid AoV, coarctation
6	Mitral atresia, DORV	23	Size of VSD and LV defined
7	Critical AS	18	Imperforate AoV, intact atrial septum
8	HLHS	22	Unicuspid AoV, coarctation
9	VSD	23	Coarctation, isthmal hypoplasia
10	Critical AS	21	Isthmal hypoplasia
11	Critical AS, arch hypoplasia	18	Extent of hypoplasia defined
12	Aortic atresia, Corr TGA	20	Coarctation
13	HLHS	18	Aorta and LV size defined
14	HLHS	19	Arch hypoplasia, coarctation
15	Severe coarctation	20	1 mm subaortic VSD
16	HLHS	19	Coarctation, arch size defined
17	HLHS	22	Tubular aortic hypoplasia
18	RV > LV, trisomy 13	20	Normal arch
19	HLHS	21	Coarctation
20	Normal heart, hydrops	26	Isthmal hypoplasia
21	HLHS, VSD	20	Two VSDs, coarctation, aortic override
22	Critical AS	20	LV size defined
23	Pulmonary atresia, IVS	23	Sinusoid identified
24	HLHS, LAI, azygos vein	18	Azygos defined
25	Critical AS	24	LV size defined
26	HLHS	19	Coarctation. 2 mm subaortic VSD
27	AVSD, DORV, LAI	19	Azygos vein defined
28	Corr TGA, aortic atresia	23	Coarctation
29	Corr TGA, Ebstein's	22	Arch hypoplasia
30	Corr TGA, Ebstein's	22	Severe coarctation
31	TGA, VSD	19	Corr TGA, severe arch hypoplasia
32	Coarctation	19	Isthmal stenosis

HLHS, hypoplastic left heart syndrome; VSD, ventricular septal defect; AS, aortic stenosis; AoV, aortic valve; DORV, double outlet right ventricle; LV, left ventricle; Corr TGA, corrected transposition of the great arteries; RV, right ventricle; IVS, intact ventricular septum; LAI, left atrial isomerism; ASVD, atrioventricular septal defect.

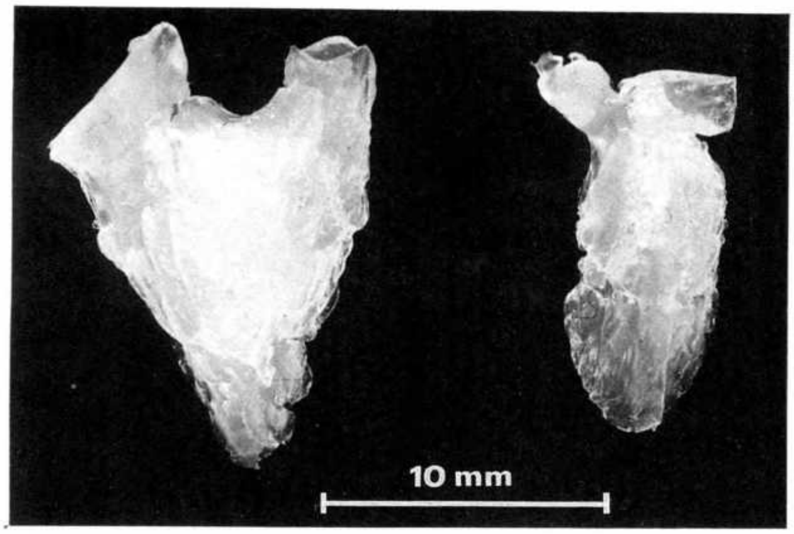


Figure 1 Casts of right and left ventricular cavities are photographed with their septal surface against the background. Morphology, shape, and size of ventricles can be compared in this case of coarctation of the aorta in a 19 week fetus.

catalysts have been used in postmortem material to study examples of congenital heart disease and to assist in the interpretation of specimens after surgical reconstruction of cardiac malformation.[6] We adapted this method for use in the analysis of cardiac abnormalities in the fetus.

Patients and methods

Three specimens of normal fetal hearts from spontaneous abortions were casted to evaluate the cardiac anatomy. Of a series of fetal specimens obtained after termination of pregnancy for congenital heart disease, 32 were selected for silicone cast injection. The gestational age of the cases studied was from 18 to 26 weeks with a mean of 20·6 weeks. Both fresh and formalin fixed specimens were used. Anatomical dissection was carried out to expose the intrathoracic organs in situ. External appraisal of the anatomy was performed. In cases where it appeared possible that casting would improve the definition of cardiovascular anatomy, a small incision was made downstream to the anatomical structure to be investigated. The incision was in the left atrium in 13, the aorta in 12, the pulmonary trunk in five, and other sites in five. Blood clots were washed out of the cavities and vessels with a water filled syringe. The casting material used was a commercially available silicone rubber sealant (Dow Corning house seal). This compound was found to be self setting over a period of one day in formalin. The material was injected gently from a syringe through a small pipette positioned in the incision. Distension of the chambers and vessels was observed as the infusion took place. In some cases, the casting material was massaged along the vessel under study until it reached the descending aorta. It was important to ensure that vessels and chambers of interest were filled with the material to avoid artefacts. The heart and lungs were removed from the thorax 24 hours after the cast injection. The cardiac anatomy was then dissected according to a standard method.[7] The cast was removed carefully from the atrium, ventricle, and great artery in progressive order, preserving the integrity of valvar tissue, papillary muscles, and small vessels.

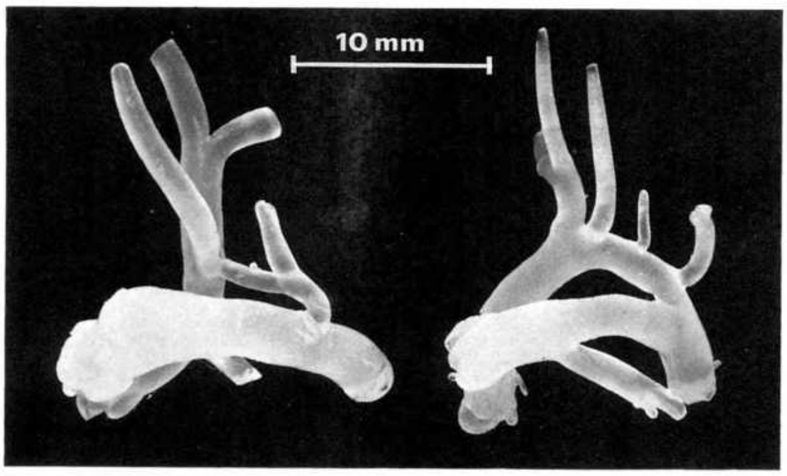


Figure 2 Arch anatomy can be compared in two fetuses of 19 weeks gestation. Coarctation of the aorta is shown on the left and a normal arch on the right. The transverse arch and arterial duct are of similar size normally with the pulmonary root slightly larger than the aorta at its origin. In this example of coarctation, the transverse arch is less than half the normal width and there is an acute angle between the isthmus and descending aorta at the site of a coarctation shelf. The origin of the pulmonary artery is nearly twice the size of the ascending aorta.

Results

Figures 1–6 illustrate some examples of the specimens that were obtained from the 35 cases. The table lists the echocardiographic diagnosis and the additional findings in the cases of congenital heart disease studied. The case illustrated in figs 1 and 2 left is one of coarctation of the aorta. The echocardiographic findings at 19 weeks of gestation were the right ventricle larger than the left; the pulmonary artery larger than the aorta; and distal arch hypoplasia in transverse sections. Figure 1 compares the casts obtained from each ventricular chamber, clearly showing the right ventricle to be nearly twice the size of the left. Figure 2 right shows a normal aorta, aortic arch, pulmonary artery, and duct in a 19 week specimen. Normally the pulmonary artery is slightly larger than the aorta but in fig 2 left, this difference is seen to be much greater than normal. The distal arch narrows considerably after the common carotid branch and the isthmus shows an acute angle at the junction between the duct and the descending aorta. The coarctation shelf indents the posterior aspect of the cast at this point. Figures 3A, B, C, and D show some of the varieties of coarctation which can occur. In the case illustrated in figure 3A, there is only a discrete shelf opposite the junction of the duct with the aorta. Figure 3B illustrates that there is isthmal hypoplasia in a fetus with a subaortic ventricular septal defect and a hypoplastic left ventricular cavity. Figure 3C shows more diffuse transverse arch hypoplasia extending from before the brachiocephalic artery to the isthmus. Figure 3D shows tubular hypoplasia from the aortic valve to the isthmus before the coarctation shelf. Figure 4 shows a whole cardiac cast with mitral atresia

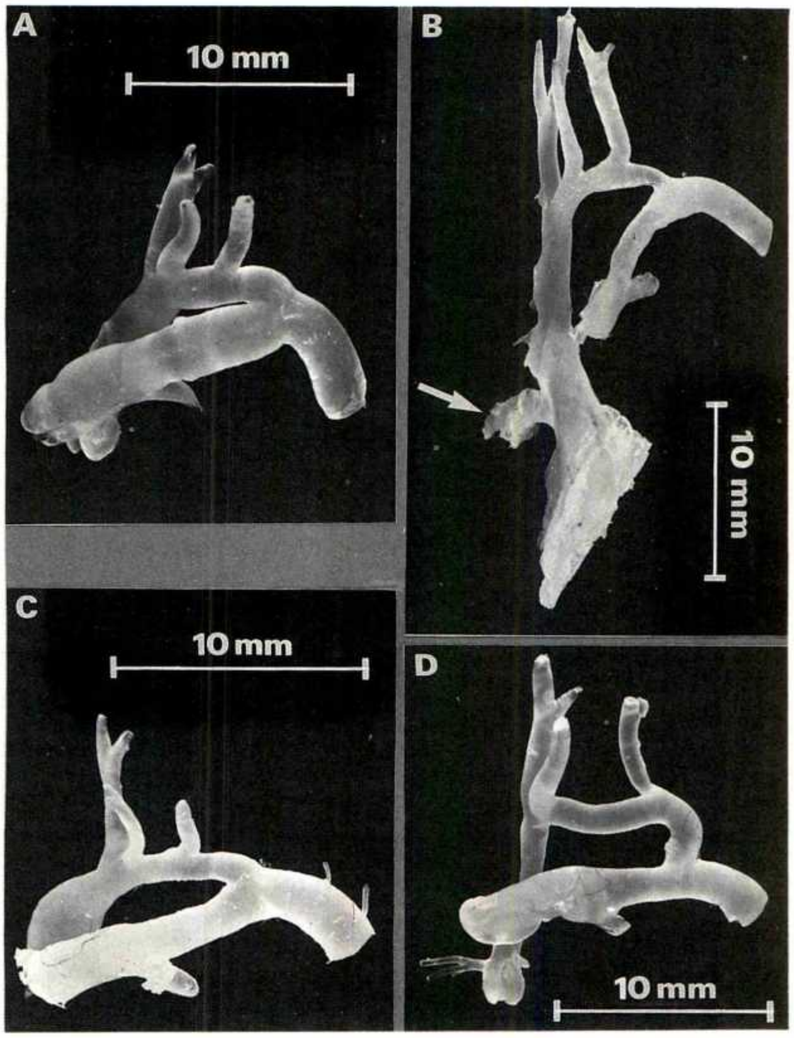
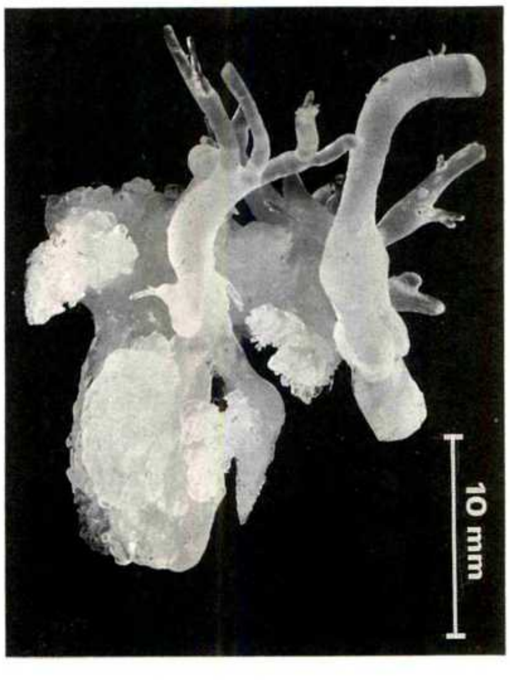


Figure 3 This series shows variation in arch abnormalities. (3A) Arch structures are of comparable sizes but a discrete coarctation shelf is seen indenting the cast in the juxtaductal position. (3B) A cast from the mitral valve to the descending aorta is shown. The left ventricle was hypoplastic although this is difficult to appreciate without the right for comparison. Cast material has crossed a subaortic ventricular septal defect (arrow). Hypoplasia of the arch is limited to the isthmus and there is a mild coarctation lesion. (3C) The arch becomes hypoplastic just before the origin of the brachiocephalic artery and remains so until the junction with the arterial duct. (3D) Tubular hypoplasia of the whole aorta to the junction with the duct is seen, most obvious in the ascending aorta.

Figure 4 Whole cardiac cast from the atria to the descending aorta. The pulmonary artery is divided at its origin and reflected to the right to display the hypoplastic left ventricle. A trabecular and subaortic ventricular septal defect are seen. The aorta arises astride the ventricular septum. The distal arch is hypoplastic and a coarctation lesion is also seen.



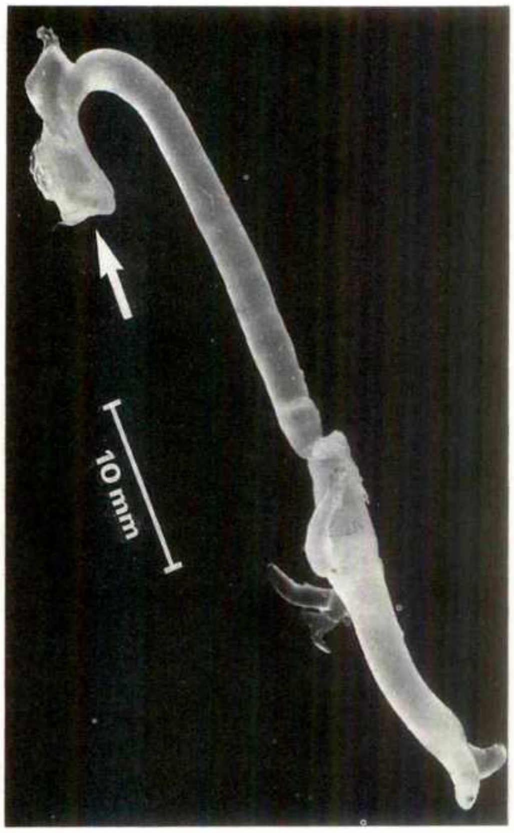


Figure 5 Renal veins are seen joining the venous system below the diaphragm. The azygos vein lay behind the aorta and connected to a left superior vena cava at its junction with the left atrium (arrow).

and left ventricular hypoplasia, and a muscular subaortic ventricular septal defect. The aorta arises astride the ventricular septum and there is transverse arch hypoplasia before a coarctation shelf. A visual understanding of the comparative ventricular sizes can be readily appreciated in the cast specimen. Figure 5 illustrates a case in which there was interruption of the inferior vena cava on echocardiographic examination of the abdominal vessels below the diaphragm in a 18 week fetus. There was a venous structure lying behind the aorta that could be seen on colour flow mapping to join a left sided superior vena cava at its junction with the left atrium. Figure 5 shows the cast of an azygos system obtained from this fetus, which correlated completely with the prenatal findings. This delicate vessel is often damaged or even destroyed on removing the thoracic viscera from the body. Figure 6 illustrates a case in which there was a hypertrophied right ventricle with a small cavity found on echocardiography at 24 weeks' gestation. The pulmonary outflow tract was atretic from the infundibulum to the pulmonary valve. The cast injection confirmed those findings but also showed a large fistulous connection between the left anterior descending coronary artery and the trabecular portion of the right ventricular cavity. Measurement of the casted structures and chambers showed a close correlation with those obtained by echocardiography in all cases where measurements were made.

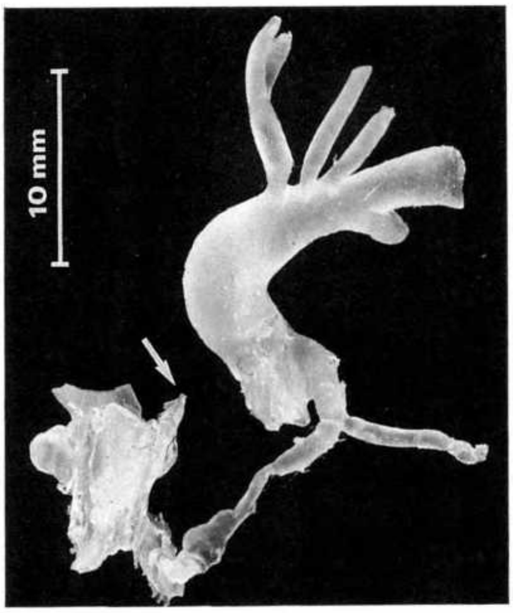


Figure 6 Small right ventricular cavity from the tricuspid valve to the atretic infundibulum (arrow). Left circumflex and anterior descending coronary arteries are seen arising from the aortic root. A sinusoidal connection between the midtrabecular portion of the right ventricle and the left anterior descending coronary artery is seen.

Discussion

This newly described technique proved particularly useful in the correlation of fetal echocardiography with pathological specimens in our series. The technique is simple and can be applied routinely. It has the advantage of maintaining the integrity of the specimen itself and producing a three dimensional picture of the cardiac cavities. Despite the small size of the fetal specimens, we achieved exquisite detail of structures less than one millimetre in size. We found that casts enhanced the interpretation of morphology, displayed paths of flow, and avoided the distortion that can occur during a standard pathological demonstration. Cast models were particularly useful as a teaching aid. Defects could be detailed in their entirety by the cast. The frequency of aortic arch lesions as underlying or associated findings in the hypoplastic left heart syndrome was demonstrated in cast material and the extent of hypoplasia of the left ventricle and arch was defined.

Echocardiographic diagnosis could be confirmed and in some cases extended—for example, in the case of the coronary artery sinusoid. More faithful representation of the cardiovascular system was obtained where casting was performed in situ; this is a practical technique in the fetal specimen. We are currently assessing the possibility of using the cast model to examine in closer detail the characteristics of valve morphology in cases of fetal valvar stenoses.

In summary, casting has proved a useful addition to the morphological analysis of fetal heart specimens. It is easy and practical to use. It provides a three dimensional model that is ideal as an aid to understanding the nature and extent of congenital heart malformations, particularly in the early fetus.

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Left ventricular performance in children: transthoracic versus transoesophageal measurement of M mode derived indices

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Abstract

***Objective*—To compare M mode derived indices of left ventricular performance obtained with transthoracic and transoesophageal echocardiography in children with congenital heart disease.**

***Design*—Transthoracic and transoesophageal M mode echocardiograms were obtained under general anaesthesia before cardiac catheterisation. Recordings were digitised by dedicated software. Indices of cavity dimension and left ventricular wall dynamics were compared.**

***Patients*—16 unselected patients with congenital heart disease.**

***Results*—Group data for simple measurements of ventricular dimension and wall thickness were similar with the two techniques and had acceptable coefficients of repeatability, but there were considerable individual differences. Correlation was poor with unacceptable repeatability for derived indices of cavity and ventricular wall dynamics.**

***Conclusion*—Both transthoracic and transoesophageal echocardiography can be used to obtain M mode derived indices of left ventricular performance but the resultant measurements are not directly comparable, presumably because of regional non-uniformity of function.**

(*Br Heart J* 1992;**87**:485–7)

With increasing availability and reduction in size of transoesophageal echocardiographic equipment transoesophageal echocardiography is rapidly becoming the imaging technique of choice in children in operating theatres, intensive care units, and during interventional cardiac catheterisation. The accurate assessment of ventricular performance is clearly important in all of these areas.

Until now the assessment of left ventricular performance with M mode echocardiography has largely been restricted to recordings obtained through the transthoracic window. It should be possible, however, to obtain potentially comparable information during transoesophageal echocardiography and the purpose of this study was to compare indices of left ventricular performance obtained from children with congenital heart disease undergoing simultaneous transthoracic and transoesophageal echocardiography.

Patients and methods

Twenty two unselected children with congenital heart disease were studied. All were undergoing cardiac catheterisation with general anaesthesia as part of their preoperative assessment. The transthoracic M mode recordings were unsatisfactory in six patients leaving 16 in whom comparative data were available. The ages of these patients ranged from three months to 17 years (median five years and four months) and their weight ranged from 4·9–55·4 kg (median 19 kg). Table 1 gives the full sequential diagnosis for each of the 16 patients.

The procedure was identical in all patients. After endotracheal intubation a transoesophageal probe was inserted. In children over 12 kg a standard adult sized 5 mHz single plane phased array transducer was used. In three patients a developmental paediatric probe was used. This had a shaft diameter of 6 mm and a switchable 7·5–5 mHz single plane phased array transducer mounted at its tip. Both probes were interfaced with a Hewlett-Packard sonus 1000 ultrasound system.

A transoesophageal gastric short axis view of the left ventricle was taken from each patient. Left ventricular M mode recordings were taken across its maximal dimension at the level of the mitral valve tips. As soon as possible after this, with the transoesophageal probe in place, a transthoracic recording of the left ventricular M mode, again at the level of the mitral valve leaflet tips, was obtained in either parasternal short axis or long axis sections. Care was taken to maintain all haemodynamic variables unchanged throughout

Table 1 Diagnoses of individual patients

Patient	*Diagnosis*
1	Pulmonary atresia with ventricular septal defect. Previous Blalock-Taussig shunt
2	Previous repair of total anomalous pulmonary venous drainage
3	Valvar aortic stenosis
4	Umbrella closure of ventricular septal defect
5	Umbrella closure of arterial duct
6	Umbrella closure of arterial duct
7	Ventricular septal defect, pulmonary hypertension
8	Supravalvar aortic stenosis, pulmonary stenosis
9	Previous repair of tetralogy of Fallot
10	Supravalve mitral membrane, subaortic stenosis
11	Double inlet left ventricle, discordant ventriculoarterial connexion, previous Fontan procedure
12	Ventricular septal defect, subaortic stenosis, mitral stenosis
13	Umbrella closure of arterial duct
14	Tunnel subaortic stenosis
15	Balloon dilatation of coarctation of aorta
16	Umbrella closure of arterial duct

Table 2 Group data (mean (SD)) for each of the indices with each technique

	Transthoracic		*Transoesophageal*	
LV Dim (max) (cm)	3·47	(0·75)	3·65	(0·79)
LV Dim (min) (cm)	2·25	(0·55)	2·43	(0·62)
SF (%)	35	(7)	33	(8)
PW (max) (cm)	1·17	(0·4)	1·04	(0·37)
PW (min) (cm)	0·74	(0·32)	0·70	(0·24)
dDim/dT/Dim (max) (s^{-1})	5·75	(1·96)	5·10	(2·05)
dDim/dT/Dim (min) (s^{-1})	−4·96	(1·65)	−4·56	(1·44)
dDim/dT (max) (cm.s^{-1})	15·00	(5·2)	14·90	(6·18)
dDim/dt (min) (cm.s^{-1})	−13·13	(3·7)	−13·25	(3·8)
dPW/dT/PW (max) (s^{-1})	5·36	(1·92)	5·63	(2·8)
dPW/dT/PW (min) (s^{-1})	−7·20	(2·9)	−6·60	(3·5)
dPW/dT (max) (cm.s^{-1})	4·73	(1·8)	4·36	(1·6)
dPW/dT (min) (cm.s^{-1})	−6·39	(2·25)	−5·17	(2·5)

LV Dim, left ventricular dimension; SF, shortening fraction; PW, posterior wall.

both recordings. A simultaneous electrocardiogram, and where possible a phonocardiogram, was recorded in each patient. All recordings were made at a paper speed of 100 mm/s.

DATA ANALYSIS

The M mode recordings were measured with a system previously described in detail.[1] Data points were taken at 10 ms intervals throughout the cardiac cycle. For each of the indices measured the mean of three consecutive beats was taken. The measurements made were: maximum left ventricular dimension (cm); minimum left ventricular dimension (cm); rate of change of ventricular dimension (cm.s^{-1}); standard rate of change of dimension (cm^{-1}); maximum posterior wall thickness (cm); minimum posterior wall thickness (cm); rate of change of posterior wall thickness (cm.s^{-1}); standardised rate of change of posterior wall thickness (s^{-1}); shortening fraction (%).

STATISTICAL ANALYSIS

All group data were expressed as mean (1 SD). Comparison of the two techniques was by linear correlation with the method of least squares, and by the coefficient of repeatability with the method of Bland and Altman.[2]

Results

Table 2 shows the group data for each of the indices, with each method. Table 3 shows the correlation coefficient between variables from each technique and the coefficient of repeatability for each index of left ventricular function.

Table 3 Comparison of methods

	Correlation coefficient	*p Value*	*Coefficient of reproducability*
LV Dim (max) (cm)	0·919	<0·01	0·62
LV Dim (min) (cm)	0·911	<0·01	0·52
SF (%)	0·78	<0·01	9·8%
PW (max) (cm)	0·885	<0·01	0·38
PW (min) (cm)	0·852	<0·01	0·34
dDim/dT/Dim (max) (s^{-1})	0·699	<0·01	3·1
dDim/dT/Dim (min) (s^{-1})	0·83	<0·01	1·8
dDim/dT (max) (cm:s^{-1})	0·53	<0·05	11·2
dDim/dt (min) (cm.s^{-1})	0·73	<0·01	5·5
dPW/dT/PW (max) (s^{-1})	0·028	NS	7·9
dPW/dT/PW (min) (s^{-1})	0·006	NS	9·9
dPW/dT (max) (cm.s^{-1})	0·55	<0·05	3·2
dPW/dT (min) (cm.s^{-1})	0·57	<0·05	4·4

See footnotes to table 2 for abbreviations.

Discussion

This study is the first to compare transthoracic and transoesophageal M mode indices of left ventricular performance in children with congenital heart disease. In general, reasonable agreement was found between the two techniques when comparing left ventricular dimensions. In particular, agreement between the two techniques for left ventricular maximum dimension, minimum dimension, and shortening fraction was good, with correlation coefficients of 0·8 ($p < 0·01$) or more and with acceptable coefficients of repeatability. Similar results have been found in adults with acquired heart disease. Comparisons of transoesophageal echo with epicardial[3] and transthoracic[4] echocardiography generally show good agreement for ventricular dimension between the two techniques. Agreement was poorer, but still acceptable, for rates of change of ventricular dimension in our patients. We also compared left ventricular wall dynamics. Whereas the two techniques showed good agreement in terms of absolute wall thickness, both maximum and minimum, there was little or no agreement between the techniques when the rate of change of wall thickening and thinning was examined. Indeed, the poor coefficient of repeatability precludes direct comparison of indices obtained with the two techniques. Furthermore, whereas there was reasonable agreement when the indices were compared, considerable variability occurred on an individual basis. Thus, although a correlation coefficient of 0·9 and an excellent coefficient of repeatability was found when comparing left ventricular maximum dimension, individual differences of over 0·5 cm were seen. This is not surprising; regional non-uniformity of ventricular dimension and function is present in the normal heart and we have shown previously that the additional structural abnormalities imposed by congenital heart abnormalities and surgery will often result in abnormalities of regional wall motion.[5,6] This presumably also accounts for the noticeable differences in ventricular wall dynamics. Here measurements are not only subject to this acquired regional non-uniformity but also will be related to anatomical differences in the area of myocardium being examined. Whereas the left ventricular posterior wall examined from a parasternal short axis view is a true posterior structure, posterior and caudal to the insertion of the posterior mitral papillary muscle, the comparable part of the ventricle recorded on the M mode echocardiogram from a gastric short axis view is more anterolateral and closer to the interventricular septum. The case for the anterior wall of the left ventricular cavity is the same. In the parasternal short or long axis section the anterior wall of the ventricular cavity is the posterior surface of the interventricular septum, whereas in the gastric short axis view it will be the more posteromedial part of the left ventricular free wall. Thus, in general, it is not possible to compare directly group or individual data from the two techniques. Our patients, however, represent a heterogeneous group. It is possible that data from a more homogeneous group would compare more favourably. Furthermore, we did not examine the reproducibility of repeated measurements from the transoesophageal approach, but it is likely that repeated measurements from either technique will provide valid data for the sequential assessment of left ventricular performance.

In summary, transoesophageal echocardiography can provide useful information about left ventricular performance. Data obtained from this technique cannot be directly compared with data obtained from transthoracic echocardiography as both group and individual variability is unpredictable.

We thank Dr D Gibson for making the digitising equipment available to us and Ms J Peatling for typing the paper.

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Br Heart J 1992;68:488–92

Transeosophageal echocardiography in neonates, infants and children: applicability and diagnostic value in everyday practice of a cardiothoracic unit

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Abstract

***Objective*—To determine the applicability of and information obtained by transeosophageal echocardiography in neonates, infants, and children in every day practice of a cardiothoracic unit.**

***Design*—Four month prospective study.**

***Setting*—Supraregional centre for paediatric cardiothoracic services.**

***Patients and methods*—58 patients aged between four days and 16 years with a wide range of cardiovascular disease underwent transoesophageal echocardiography under sedation or general anaesthetic. One of two paediatric probes (6 or 7 mm diameter), or an adult probe (13 mm in diameter) was used. Whenever possible the investigation was immediately preceded by precordial echocardiography.**

***Main outcome measures*—Success, failure, technical difficulties, and complications of probe introduction and, when possible, comparison of the information obtained with that obtained from precordial echocardiography.**

***Results*—Introduction of the probe was successful in 57 of the 58 patients. The only complication encountered was transient bradycardia during manipulation of the probe in a 2·2 kg baby. The adult (13 mm) probe was successfully used in children as small as 7·0 kg. Below this weight a smaller paediatric probe was required. In 56% of cases transoesophageal ultrasound provided information not obtained from the precordial approach. The technique was of particular value perioperatively and in the immediate postoperative period in neonates and infants and in the presence of valve prostheses and the investigation of mediastinal tumours in older children.**

***Conclusions*—Transoesophageal echocardiography is a valuable additional investigative tool for children of all ages. It is of particular value when aquisition of precordial image is impaired around the time of and after operation and in children with prosthetic valves or mediastinal tumour. Image quality was superior with the adult probe and we recommend the use of this probe unless the patient's weight is below 7 kg, when a paediatric probe allows this technique to be used usefully and safely in babies as small as 2·2 kg.**

(*Br Heart J* 1992;68:488–92)

Transoesophageal echocardiography is a well established technique in adults. Studies in children have been limited in the main to older subjects undergoing surgical repair of congenital cardiac defects and in the assessment of a variety of specific cardiac defects, usually in the cardiac catherisation laboratory. The role of the transoesophageal approach remains uncertain outside the operating theatre, especially in children under 20 kg.

Study of small children has become possible with the development of smaller transducers and we report our initial experience with the use and application of newly available paediatric transducers as well as adult transducers in a population of children with a wide range of age and pathology.

Patients and methods

Fifty eight children aged between 4 days and 16 years whose weights ranged from 2 to 63 kg were studied. Thirty one of the children were under 5 years of age. Table 1 summarises the clinical settings of each investigation. Thirty nine children had congenital heart disease of whom 28 had undergone surgical treatment including one who was studied shortly after cardiac transplantation. Seven of the children had prosthetic heart valves (five mitral, two aortic), of whom four were studied in the immediate postoperative period, two because of late development of prosthetic valve regurgitation and one because of suspected endocarditis. Intraoperative assessment was made in one child during surgery for obstructive hypertrophic cardiomyopathy. Echocardiographic study in the cases of suspected endocarditis was made before the availability of results of blood culture.

Twenty eight of the children were investigated under sedation and were ventilated on the intensive care unit, 25 of these were in the early postoperative period. Twenty seven children were under general anaesthesia either in the catheter laboratory or the operating theatre and the remaining three studies were performed under intravenous sedation alone with midazolam. Paediatric transducers (Hewlett

Table 1 Demographic data

Clinical setting	*No of cases*	*Age range*
Early postoperative period	25	4 days–16 yr
Diagnostic catheterisation	14	3–14 yr
Suspected endocarditis	7	5 mth–14 yr
Interventional catheterisation	5	4–14 yr
Mediastinal tumour or trauma	3	6–15 yr
Late prosthetic valve evaluation	2	16 yr
Tricuspid valve abnormality	1	6 yr
Intra-operative (hypertrophic cardiomyopathy)	1	9 yr

Packard or Aloka with respective diameters of 6 mm and 7 mm) were used in 21 of the examinations and a standard adult transducer of diameter 13 mm (Hewlett Packard) was used in 37.

Introduction of the probe in very young children was often facilitated by guiding the transducer tip into the upper oesophagus with a finger placed on the epiglottis. Precordial echocardiograms were performed in 52 cases immediately before the transoesophageal study, and the results of the two investigations were compared. Six children did not have precordial studies performed immediately before transoesophageal study because of restricted access to the chest wall in the theatre or catheter laboratory.

Results

Transoesophageal echocardiography was successfully performed in 57 of the 58 children; the one failure was due to inability to pass the probe into the oesophagus of a 2 kg baby with an endotracheal tube in place. The paediatric probes were used in children ranging from 2·2 to 13·5 kg and the adult probe in others ranging from 7·0 to 63 kg. The only adverse effect of probe introduction was transient bradycardia during manipulation of the probe in a 2·2 kg baby. The investigation was none the less completed by reducing movement of the probe to a minimum. Transoesophageal images that added diagnostic information to images obtained from the precordium were obtained in 29 (56%) of the 52 cases who had the two studies performed nearly simultaneously (table 2).

EARLY POSTOPERATIVE STUDIES

Six patients were studied to assess ventricular function because of poor clinical progress associated with low cardiac output. In five of these, including one cardiac transplant recipient, precordial images were inadequate due to mediastinal air and the position of drains. In all six cases clear images were obtained with the transoesophageal approach, even when the sternum had been left open. In one child extremely poor left ventricular function was found along with a mobile blood clot in the left ventricle that was invisible on precordial study. Four patients were investigated to assess prosthetic valve function; one had undergone emergency valve replacement for endocarditis. In all four cases there were regurgitant jets that had not been seen in the precordial study. Four children were investigated to assess repair of ventricular or atrioventricular septal defect, and although transoesophageal image quality was high, it did not provide any useful additional information when compared with the precordial study. Three patients were studied to assess venous return after Senning operation (2) or repair of total anomalous pulmonary venous drainage (1).[2] Precordial echo image quality in these was poor, but the transoesophageal approach showed clear pulmonary and systemic venous channels and flow patterns (fig 1) in the children with transposition, and detection of pulmonary venous obstruction (leading to reoperation) in the child with anomalous pulmonary venous drainage. Assessment after Fontan operation in one child gave detailed images of the atriopulmonary anastomosis which was not possible precordially due to mediastinal air. This was also the case in a patient after correction of double outlet right ventricle with pulmonary stenosis, where transoesophageal study showed a good surgical result but also a small shunt from the coronary sinus to the left atrium that had not been appreciated at cardiac catheterisation and angiography.

Three children were studied to assess patency of aortopulmonary shunts but this was only possible in one case by transoesophageal echocardiography, where a central shunt had been used. Similarly after repair of coarctation of the aorta, the transoesphageal approach failed to add any additional information.

SUSPECTED BACTERIAL ENDOCARDITIS

Of the seven patients with suspected endolcarditis, three subsequently had positive blood cultures (one with ventricular septal defect, one with aortic valve replacement and one with a right Blalock-Taussig shunt). No vegetations were seen at precordial echocardiography in these cases, but the transoesophageal approach showed vegetations on the ventricular septum in the first case and on the aortic valve prosthesis in the second. Although shunt flow in the right pulmonary artery was clearly seen with colour flow Doppler in the third case, anatomical detail of the shunt was not visible and no vegetations were seen. In another child with a Blalock-Taussig shunt we were again unable to get an image of the shunt itself, even in its distal part.

Table 2 A summary of the 29 cases in which transoesophageal imaging provided information unavailable from precordial echocardiography. Results from both imaging approaches were compared in the 52 children who underwent near simultaneous precordial and transoesophageal study

Clinical setting	*No of cases*	*Additional information from transoesophageal study*
Early postoperative period	12	Imaging of intracardiac venous pathways, evaluation of ventricular function, detection of intracardiac thrombus, detection of paraprosthetic mitral regurgitation.
Diagnostic catheterisation	9	Imaging of intracardiac venous pathways, assessment of atrial shunts, assessment of subaortic stenosis.
Mediastinal mass or trauma	3	Extensive cardiac infiltration detected, extent of right atrial tumour clearly seen, useful in guiding transvenous biopsy of right atrial mass, diagnosis of aortic rupture and mediastinal haematoma.
Suspected endocarditis	2	Vegetations seen in both cases.
Late prosthetic valve malfunction	2	Detection of aortic prosthesis dehiscence, valve regurgitation.
Suspected tricuspid valve abnormality	1	Tricuspid chordal attachments clearly traced.

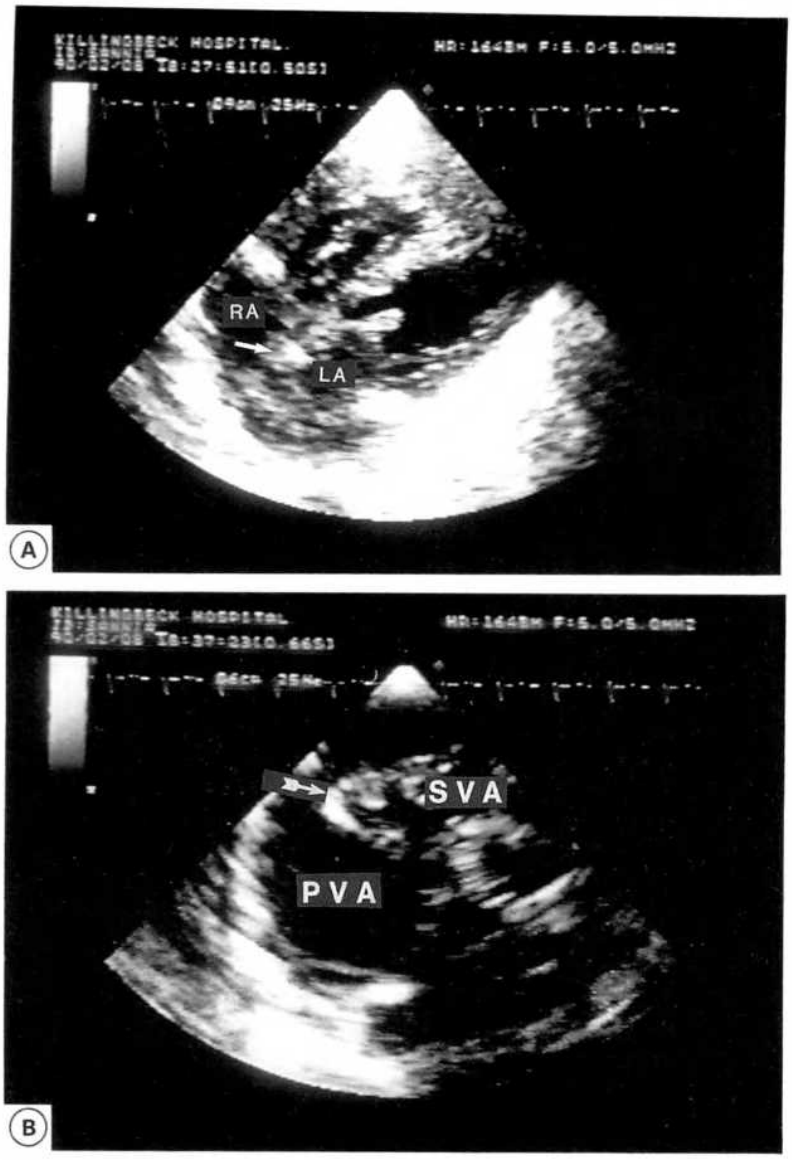

Figure 1 (A) Cross sectional echocardiogram in a modified subcostal, four chamber view in a four month old child after a Senning operation showing typical image quality 48 hours after median sternotomy. The intra-atrial baffle (arrowed) is only just visible. (B) The same heart imaged from the transoesophageal approach. The venous channels, their dimensions and the intra-atrial baffle are clearly seen (arrowed), (PVA, pulmonary venous atrium; SVA, systemic venous atrium).

DURING CARDIAC CATHETERISATION

Interventional catheter procedures

Transoesophageal echocardiography was performed during balloon dilatation of the pulmonary valve (two cases), the aortic valve (one case), stenosis of the systemic venous channel after a Mustard operation for transposition of the great arteries (one case), and during pericardiocentesis (one case). Measurement of the aortic and pulmonary roots in the first three cases was easy with the high quality image obtained by transoesophageal ultrasound. The position of the balloon was clearly seen in all four cases, and valve regurgitation was rapidly detectable after balloon deflation. Overall, however, the technique was of limited help in the overall procedure of balloon dilatation of valves with the possible exception that it may have reduced radiological screening time during balloon positioning. Accurate positioning of the balloon in the intra-atrial stenosis in the patient with a Mustard operation was, however, facilitiated by transoesophageal imaging and widening of the venous channel (seen particularly well with colour flow imaging) was clearly recognisable immediately after balloon deflation. Before pericardial drainage transoesophageal imaging allowed the posterior pericardium to be clearly seen in a search for a tumour, and needle tip position was fairly easily monitored, although this probably contributed little to the safety of the procedure.

Diagnostic catheter procedures

In six patients precordial imaging showed dilatation of the right heart chambers but no apparent cause. Three had clinical signs suggesting atrial septal defect. In two cases transoesophageal echocardiography showed sinus venosus atrial septal defects with associated anomolous pulmonary venous drainage in one. In the other four, the only abnormality at transoesophageal study was a patient oval fossa with very small left to right shunts in each case. This negated the need to proceed to a catheter study.

Two patients had suspected obstruction of the pulmonary venous channel after Sennings operations and in each case transoesophageal echocardiography provided more detailed images of the pulmonary venous channels than did the precordial approach. In one instance transoesophageal Doppler echocardiography enabled detailed anatomical assessment of the obstruction where precordial Doppler had failed and in the other it showed a small baffle leak not found precordially.

In two children with complex cardiac defects transoesophageal study gave anatomical information about the atrioventricular valves not apparent from the precordium. This led to diagnosis of a straddling AV valve in one case and a double orifice mitral valve in the other.

Improved morphological assessment of subaortic stenosis was documented in one child.

MEDIASTINAL PATHOLOGY AND TUMOURS

In a child with extensive trauma of the head and neck precordial echocardiography was normal but the transoesophageal study showed an intimal flap in the descending thoracic aorta and posterior mediastinal haematoma due to dissection and rupture of the aorta, prompting urgent surgical treatment. In a child with precordial echocardiographic findings of an intra-atrial mass, transoesophageal study showed better the extent of the tumour in the right atrium and allowed guided biopsy of the tumour. In a child presenting with acute breathlessness and clinical signs of pulmonary hypertension the transoesophageal study showed extensive mediastinal tumour surrounding the branch pulmonary arteries and extensive invasion of the atrial walls and atrial septum; the only abnormality visible on the precordial study was right ventricular hypertrophy and dilatation (fig 2).

LATE PROSTHETIC VALVE MALFUNCTION

Partial dehiscence of an aortic valve after an

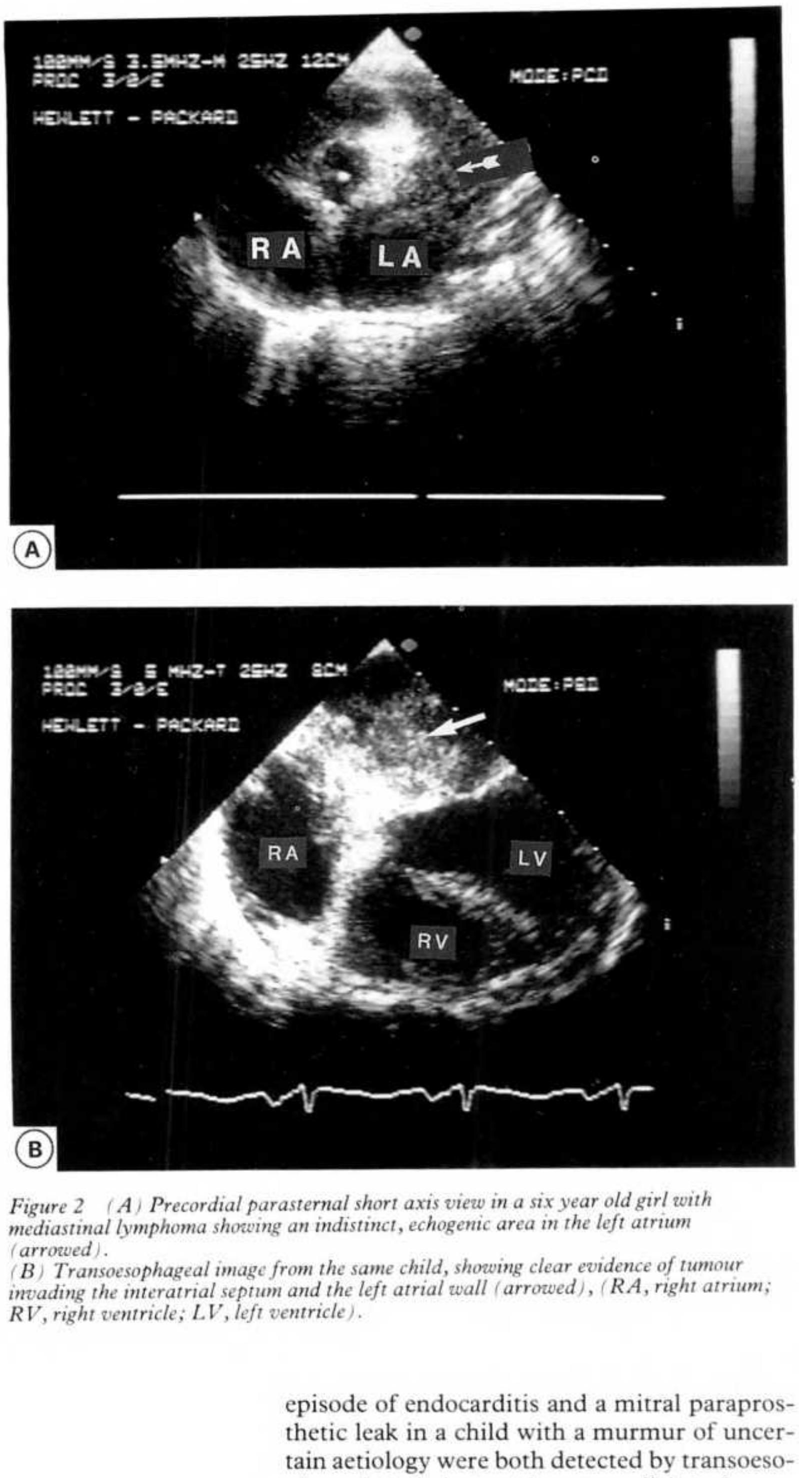

Figure 2 (*A*) *Precordial parasternal short axis view in a six year old girl with mediastinal lymphoma showing an indistinct, echogenic area in the left atrium (arrowed).*
(*B*) *Transoesophageal image from the same child, showing clear evidence of tumour invading the interatrial septum and the left atrial wall (arrowed), (RA, right atrium; RV, right ventricle; LV, left ventricle).*

episode of endocarditis and a mitral paraprosthetic leak in a child with a murmur of uncertain aetiology were both detected by transoesophageal study but not by precordial study.

STUDIES BEFORE AND DURING OPERATION

In a case of transposition of the great arteries and ventricular septal defect precordial echocardiography of suboptimal image quality had suggested the possibility of straddling of the tricuspid valve. Transoesophageal study allowed detailed inspection of the chordal anatomy that was normal. Perioperative transoesophageal study of a three year old undergoing left ventricular outflow resection for hypertrophic cardiomyopathy and mitral regurgitation allowed monitoring of the effect of muscle resection, which was accompanied by dramatic improvement in severity of mitral regurgitation detected by colour flow imaging. An elective decision to replace the mitral valve was abandoned and the mitral valve was conserved with an excellent postoperative result.

Discussion

Transoesophageal echocardiography is well established in the investigation of adult native and prosthetic valve regurgitation,[1] in the detection of vegetations and other consequences of bacterial endocarditis,[2] in the evaluation of thoracic aortic pathology,[3] in intraoperative monitoring of left ventricular function,[4] and in valve repair.[5]

In children studies have concentrated mainly on intraoperative assessment of surgical correction of congenital heart disease[6 7] and most studies have been limited to older children due to the size of the widely available adult transoesophageal probes.[8] More recently transoesophageal imaging has been found of benefit in the assessment of fixed subaortic obstruction,[9] after Fontan operations,[10] and in the assessment of anomolous systemic and pulmonary venous connections.[11] The advent of smaller probes has extended the potential use of the technique to younger age groups but the indications for study in children less than 20 kg remains to be defined.[12]

We were able to examine a child of 2·2 kg with the 7 mm diameter probe although we were unsuccessful in a 2 kg baby, largely due to the presence of an endotracheal tube. The smallest child studied with the 13 mm adult probe was 7·0 kg showing that adult equipment may be used safely in comparatively small children. The procedure was well tolerated and clear images of the heart and great vessels were obtained in all cases, often providing information that was unobtainable from a standard precordial echocardiogram. This was particularly the case in the immediate postoperative period when precordial imaging was hampered by the presence of mediastinal air; transoesophageal study allowed rapid assessment of ventricular function and the results of surgical repair. Notable examples were the assessment of systemic or pulmonary venous flow after surgical redirection, early detection of infective vegetations, and the detection of prosthetic valve regurgitation. The technique also enables echocardiographic monitoring during surgery or interventional catheterisation, providing rapid functional assessment of the procedure and complementing radiographic screening and angiography in balloon positioning, possibly making a contribution to the reduction of *x* ray exposure to both patient and operator. We found this particularly useful in intra-atrial stenosis after the Mustard operation because of the high quality images obtained of the atrial anatomy. In the child with mediastinal lymphoma full sight of the extent and invasion of the tumour was possible only by the transoesophageal approach. Disappointingly peripheral systemic to pulmonary shunts were usually beyond the reach of the transoesophageal approach.

Transoesophageal echocardiography is feasible and well tolerated even in the neonate and it frequently provides information which is unobtainable by precordial study. The 13 mm probe can be safely passed in children as small as 7 kg but for those under this weight, a paediatric probe should be used and this will allow investigation of babies as small as 2·2 kg.

It is therefore of value in children under certain circumstances—namely, in the immediate postoperative period, in the presence of prosthetic valves and atrial or mediastinal pathology, or suspected endocarditis, where the benefits are the same as for adult patients.

This study was supported by The National Heart Research Fund and the Killingbeck Children's Heart Surgery Fund. We are grateful for the technical support of Keymed Aloka and Hewlett-Packard.

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Comparative value of transthoracic and transoesophageal echocardiography before balloon dilatation of the mitral valve

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Abstract

***Objective*—To assess the relative merits of transthoracic and transoesophageal echocardiography before balloon dilatation of the mitral valve.**

***Design*—Transthoracic and transoesophageal echocardiograms were prospectively performed in 35 patients being considered for balloon dilatation of the mitral valve. Echocardiograms were analysed for image quality, the assessment of valve morphology, the detection of left atrial thrombus, and the assessment of mitral regurgitation and other valvar pathology.**

***Patients*—35 consecutive patients with symptomatic dominant mitral stenosis.**

***Interventions*—30 eventually underwent balloon dilatation of the mitral valve by the Inoue technique. Five patients had mitral valve replacement.**

***Main outcome measures*—Echocardiographic and surgical detection of left atrial thrombus and successful, uncomplicated balloon dilatation of the mitral valve.**

***Results*—Left atrial thrombus was detected in 1/35 patients by transthoracic studies compared with 6/35 from transoesophageal studies. Otherwise both techniques gave comparable results. Thrombus was confirmed at mitral valve replacement in five patients. Successful dilatation of the mitral valve was performed in 30 patients.**

***Conclusions*—Transthoracic echocardiography is a useful screening procedure but transoesophageal echocardiography is mandatory before balloon dilatation of the mitral valve for the detection of left atrial thrombus.**

(*Br Heart J* 1992;68:493–7)

Transvenous balloon dilatation of the mitral valve is now well established as an alternative to surgery in a selected group of patients with symptomatic dominant mitral stenosis.[1] Various techniques have been used, but all transvenous methods involve manipulation of at least one guide wire and balloon within the left atrium before balloon inflation across the mitral valve.[2-5] Widely recognised contraindications to the procedure include left atrial thrombus, significant mitral regurgitation, excessive valvar or subvalvar calcification, and significant pathology in other valves such as aortic regurgitation.[6] Echocardiography plays a vital part in assessing the suitability of patients for balloon dilatation of the mitral valve.[6 7] It has been our policy for some time to carry out both transthoracic and transoesophageal echocardiography before dilatation of the mitral valve. The aim of this study was to evaluate the relative merits of the two techniques before balloon dilatation.

Patients and methods

PATIENTS

Thirty five consecutive patients who were being considered for balloon dilatation of the mitral valve were studied. Patients had been referred from within and outside our institution on the basis of clinical history, clinical examination, and baseline investigations including a transthoracic echocardiogram. The group consisted of 20 women and 15 men. The mean age was 62 (range 22–78) years. Twenty four patients were in atrial fibrillation and 11 in sinus rhythm. Thirty two of the 35 patients were receiving warfarin and all these patients had a prothrombin time of > 1·5 times that of controls. Five patients had a history of arterial embolic events. Two had had transient ischaemic attacks, one a cerebrovascular accident, and two a femoral embolus.

BALLOON DILATATION OF THE MITRAL VALVE

The Inoue system was used for all cases in this study. The technique has been described in detail elsewhere.[2] Briefly, a safety J guide wire is positioned within the left atrium after a standard Brockenbrough interatrial septal puncture. The Inoue balloon is then positioned within the left atrium before being guided by flow across the mitral valve for subsequent inflation. With this technique no guide wires are positioned within the left ventricular cavity.

ECHOCARDIOGRAPHY

All echocardiograms carried out during this study were performed by one of three operators experienced in both transthoracic and transoesophageal echocardiography.

Transthoracic echocardiography

Transthoracic echocardiography was performed with a Hewlett-Packard 77020 Phased-Array Scanner with a 2·5-MHZ transducer.

Pulsed wave, continuous, and colour flow Doppler were used in all studies.

Transoesophageal echocardiography

Transoesophageal echocardiography was performed with the same Hewlett-Packard system and a 5 MHZ single plane oesophageal transducer with colour flow Doppler.

Each patient underwent transthoracic and transoesophageal echocardiography on the same day, generally immediately before the proposed valve dilatation and always within one month of balloon dilatation of the mitral valve.

Results

All echocardiograms were analysed independently by two experienced people blinded to the subsequent clinical course of the patient. In the event of disagreement a third observer was used and the result determined by a consensus.

The variables analysed were: image quality; valvar morphology and mitral valve area; left atrial thrombus; mitral regurgitation; other significant lesions—for example, pulmonary hypertension and other valvar lesions.

IMAGE QUALITY

Some subjectivity in the assessment of image quality is unavoidable. Image quality from each study was scored on a scale of 1 to 5, 1 being a very poor image and 5 high quality definition.[8] An aggregate score of 6 or above (by the two operators carrying out the analysis) was regarded as optimal imaging while any score below this was regarded as suboptimal. Imaging was suboptimal in 6/35 transthoracic echocardiographic images. In all cases this was due to a respiratory artefact and in none of these cases could the mitral valve area be reliably planimetered in the short axis view. Image quality for transoesophageal echocardiography was suboptimal in 4/35. Invariably this was due to a greatly enlarged left atrium that caused displacement of the transducer and created difficulty in adequately aligning the left atrium, mitral valve, and left ventricle (fig 1).

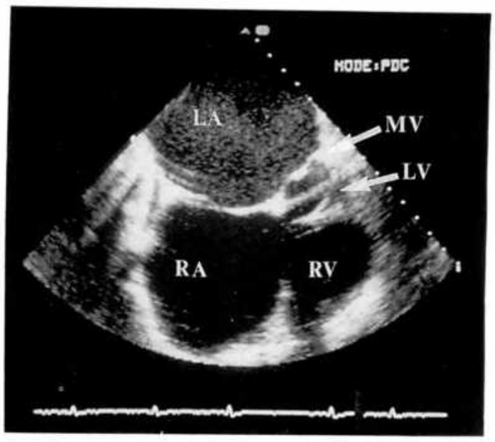

Figure 1 Transoesophageal four chamber image shows the difficulties in imaging the mitral valve when there is a greatly enlarged left atrium. Morphological assessment of the mitral valve (MV) and alignment of the left atrium (LA), MV, and left ventricle (LV) for colour flow studies is obviously unsatisfactory. This is caused by displacement of the transducer leading to horizontal rather than vertical alignment of the right and left heart. RA, right atrium; RV, right ventricle.

VALVE MORPHOLOGY AND MITRAL VALVE AREA

An echocardiographic score before balloon dilatation (as used by others) was used to assess valve morphology.[7] With this system scores of 0 to 4 are assigned to leaflet mobility, thickening, calcification, and subvalvar thickening; higher scores represent increasing morphological abnormalities. Patients with a score of 8 or less are usually excellent candidates for dilatation whereas those with a score of 10 or more have increased complications and a lower success rate.[6] There was no statistical difference in the mean (SD) echocardiographic score for the two groups. This was 7·7 (1·8) for transthoracic echocardiography and 7·3 (1·6) for transoesophageal echocardiography. In five patients, however, leaflet calcification was limited to the leaflet tips on transoesophageal studies whereas calcification had seemed more extensive during transthoracic studies. Figure 2 shows the ease with which valvar and subvalvar calcification can be assessed during transoesophageal studies.

Mitral valve area, whether assessed by the pressure half time method[9] or by planimetry, could only be assessed by transthoracic echocardiography. Mean mitral valve area before dilatation was 1·03 (0·3) cm^2 by pressure half time (n = 35) and 1·1 (0·3) cm^2 by planimetry (n = 29). Commisural fusion could also only be assessed by transthoracic echocardiography; as for mitral area this was because a reliable short axis view across the mitral valve with the single plane oesophageal transducer was difficult to obtain. The transthoracic short axis view remains an important image before dilatation as it provides a baseline from which changes may be measured after serial balloon inflations during the procedure.

LEFT ATRIAL THROMBUS

Thrombus was identified in 1/35 from transthoracic echocardiography compared with 6/35

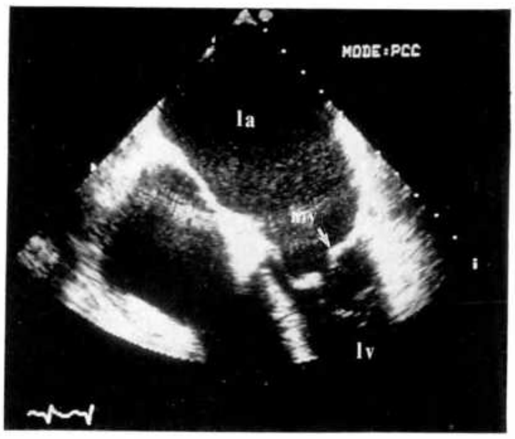

Figure 2 More usual image obtained in the transoesophageal four chamber view compared with figure 1. The left and right heart now lie in a vertical plane and the ease with which mitral valve (mv) valvar, and subvalvular calcification can be assessed. Alignment of the left atrium (la), mv, and left ventricle (lv) is also ideal for colour flow Doppler studies.

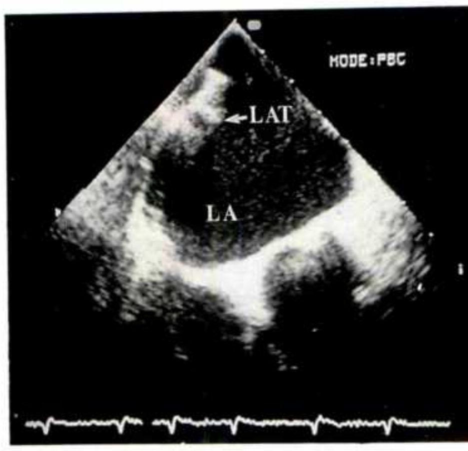

Figure 3 Example of left atrial thrombus (LAT) seen during transoesophageal echocardiography. No thrombus was seen during the transthoracic study in this case. The image shows LAT within the body of the left atrium (LA) in the basal short axis view. There is associated spontaneous echo contrast within the body of the LA.

from transoesophageal echocardiography. During transoesophageal studies this was localised to the body of the left atrium in four patients, to the left atrial appendage in one patient, and to both sites in a further patient. Figure 3 shows an example of left atrial thrombus seen during transoesophageal echocardiography. No thrombus was seen during the transthoracic study in this patient. All six patients in whom left atrial thrombus was seen were in atrial fibrillation and receiving anticoagulation treatment.

Three of the six patients with left atrial thrombus had a history of arterial emboli (one cerebrovascular accident, one transient ischaemic attack, and one femoral embolus). Two further patients with a similar history (one transient ischaemic attack and one femoral embolus) had no left atrial thrombus identified. One patient who had organised thrombus within the left atrial appendage, and who was not considered to be fit for mitral valve replacement, did proceed to balloon dilatation of the mitral valve. Mitral valve dilatation was cancelled in the other five patients with left atrial thrombus and they subsequently underwent mitral valve replacement.

Transoesophageal echocardiographic studies alone therefore led to the cancellation of four cases (thrombus seen in one patient during transthoracic studies) who would have proceeded to dilatation of the mitral valve on the basis of the transthoracic study alone. Left atrial thrombus was confirmed in all five patients who underwent mitral valve replacement.

MITRAL REGURGITATION

Transthoracic echocardiography with continuous and colour flow Doppler allowed mitral regurgitation to be graded on the basis of the maximum distance from the valve orifice attained by the regurgitant signal and on the area covered by the regurgitant signal.[10] The grading could also be modified by the width of the colour flow jet at the valve orifice, the intensity and timing of the continuous wave Doppler signal, and the proximetry of the jet to a left atrial wall. A similar form of this grading system, as validated by others, was also used for transoesophageal studies.[11] Analysis of the pulsed wave Doppler signal of pulmonary venous flow was also used in the assessment of mitral regurgitation during transoesophageal studies.

With this grading system 16/35 patients had mild mitral regurgitation on transthoracic echocardiography. Transoesophageal echocardiography did not alter the grading in any of these patients. A further 10 patients had minimal mitral regurgitation with transoesophageal echocardiography. Transoesophageal echocardiography was particularly useful in assessing eccentric mitral regurgitation, when the ability to sample pulmonary venous flow by pulsed Doppler echocardiography provided important additional information. It is recognised that under circumstances in which regurgitant jets impinge on the atrial wall colour flow mapping alone may underestimate the degree of mitral regurgitation.[12]

Mitral regurgitation during subsequent left ventriculography was graded by the method of Sellers *et al.*[13] Thirty four of the 35 patients had grade 1+ mitral regurgitation or less, while one patient had 2+ mitral regurgitation.

ASSESSMENT OF OTHER IMPORTANT LESIONS

Pulmonary hypertension

From transthoracic echocardiography with continuous wave Doppler 12/35 patients had tricuspid regurgitation and an adequate Doppler envelope for the estimation of systolic pulmonary artery pressures.

Other valvar lesions

Eight patients had mild aortic valve disease, which could be quantitatively assessed by transthoracic echocardiography with continuous wave Doppler. Pulsed wave Doppler showing no reversed flow in the descending aorta could also be used in the assessment of aortic regurgitation.[14]

In our experience, the alignment of the colour flow Doppler jets of both tricuspid and aortic valve disease is difficult with the single plane transoesophageal probe.

CLINICAL OUTCOME

Thirty of the 35 patients went on to successful balloon dilatation of the mitral valve. Mean mitral valve area, calculated by planimetry when possible, after the procedure was 1·91 (0·38) cm^2, and 27 (90%) patients had an area after dilatation > 1·5 cm^2, which has traditionally been classed as an optimal result. No patient developed > 2+ mitral regurgitation, and no patient experienced an embolic event during the procedure.

Five patients underwent mitral valve replacement and in all these patients left atrial thrombus was confirmed at surgery.

Discussion

Transvenous balloon dilatation of the mitral valve provides an attractive alternative to surgery in patients with mitral stenosis. However, the procedure is not without risk; arterial embolus is the most catastrophic of the potential complications of the procedure. The incidence of left atrial thrombus, diagnosed by transoesophageal echocardiography, in this study was 17% and is in line with previous reports of 15%–22% in two large series of patients with mitral valve disease.[15 16] Two previous studies have used transoesophageal echocardiography to report an incidence of left atrial thrombus of 26% (5/19) and 10% (2/20) in patients being considered for balloon dilatation of the mitral valve.[17 18] Our study is the largest reported to date in English publications and the first to report the experience of a United Kingdom centre. It also compares all the echocardiographic data obtained before dilatation with the transthoracic and the single plane transoesophageal approach.

All transvenous valve dilatation techniques, whether with the flow guided Inoue balloon or the wire guided single and double balloons, require some guide wire and balloon manipulation within the left atrium with the risk of dislodging a thrombus. Before the availability of transoesophageal echocardiography, transthoracic echocardiography was the investigation of choice in assessing the suitability of patients for mitral valve dilatation. This imaging technique, however, is known to be unreliable in detecting thrombus within the body of the left atrium, and the left atrial appendage is usually not seen. Vahanian *et al*, in a series of 212 patients being considered for mitral valve dilatation, excluded only one patient, because of the detection of left atrial thrombus by transthoracic echocardiography.[19] The reported incidence, to date, of arterial emboli during balloon dilatation of the mitral valve is 2%–4%.[19–21]

Transoesophageal echocardiography now provides a sensitive means of interrogating the left atrium and left atrial appendage. The procedure, however, is semi-invasive and involves a variable amount of discomfort to the patient. Because of this, clear clinical benefit to the patient should be shown before it is introduced into routine practice before mitral valve dilatation. In this study transoesophageal echocardiography alone led to a change in the clinical management of the patient in six (17%) patients. In four patients valve dilatation was cancelled because of evidence of left atrial thrombus, whereas in two patients valve dilatation was allowed to proceed when no left atrial thrombus was seen despite a clear history of arterial emboli.

There were no embolic episodes during balloon dilatation of the mitral valve in this series of patients. Before the introduction of routine predilatation transoesophageal echocardiography 33 patients underwent mitral valve dilatation at our hospital (all performed by the same operator). Three patients in this group had transient ischaemic attacks during the procedure. Comparison of the two groups (those with and those without predilatation transoesophageal echocardiography) is, however, difficult because: (*a*) the first 27 cases were performed by the over the wire technique with single or double balloons. The potential for embolic episodes may be higher in these patients because of increased wire and balloon manipulation in the left atrium and the longer inflation to deflation times of these balloons. All arterial emboli occurred in this group of patients; (*b*) the learning curve of the operator may have increased the complication rate in this group.

Apart from the assessment of left atrial thrombus, transthoracic echocardiography appeared to compare favourably with the transoesophageal approach. Indeed transthoracic studies had a number of advantages over the single plane transoesophageal images especially in terms of the assessment of mitral valve area and commissural anatomy, and in enabling the monitoring of the results of serial balloon inflations during the procedure. The excellent correlation between mitral regurgitation assessed by echocardiography and left ventricular angiography may represent an under referral of patients with anything other than very mild mitral regurgitation by the transthoracic route.

STUDY LIMITATIONS

A single plane transoesophageal system without the facility for on line continuous wave Doppler examination was used for the transoesophageal studies in this series. The newer biplane and multiplane transducers may well have a number of advantages over this system and should allow better images of the left atrium and mitral valve apparatus and the assessment of mitral valve area. These advantages, however, are still undergoing clinical evaluation and the oesophageal transducers are not yet widely available.

A definite reduction in arterial emboli, due to the introduction of transoesophageal echocardiography, cannot be claimed as the two groups undergoing mitral valve dilatation (those with, and those without transoesophageal echocardiography) are not strictly comparable. We have, however, had no embolic events during balloon dilatation of the mitral valve since the introduction of the Inoue technique combined with the routine transoesophageal assessment of patients before valve dilatation.

Conclusion

Transthoracic and transoesophageal echocardiography give complimentary information before balloon dilatation of the mitral valve. Transthoracic studies are useful as a screening investigation in the process of assessing the suitability of patients for balloon dilatation of the mitral valve and adequately evaluates mitral regurgitation, valve morphology, mitral valve area, and the presence of other valvar lesions. The transthoracic approach also supplies important baseline images and measurements that can then be followed up after serial balloon inflations during the procedure. Transthoracic echocardiography, however, will fail to diagnose important left atrial thrombus in a significant number of patients and, therefore, transoesophageal echocardiography is mandatory before balloon dilatation of the mitral valve to identify these high risk patients. With the introduction of this technique into routine clinical practice the risk of dislodging left atrial thrombus during mitral valve dilatation should be reduced.

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Echocardiographic demonstration of important abnormalities of the mitral valve in congenitally corrected transposition

Daniel J Penny, Jane Somerville, Andrew N Redington

Abstract

Whereas abnormalities of the morphological tricuspid valve are common in the setting of discordant atrioventricular connections, there are only a few postmortem reports of abnormalities of the mitral valve in this condition. This report describes two patients with discordant atrioventricular connections, in whom important abnormalities of the mitral valve were found during life by cross sectional echocardiography.

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There are few reports of abnormalities of the morphological mitral valve in patients with congenitally corrected transposition of the great arteries. Furthermore, it has been suggested that when present, these abnormalities are likely to be clinically unimportant.[1] We have recently seen two patients with congenitally corrected transposition of the great arteries, both of whom were found to have important abnormalities of the mitral valve. It is unusual for these abnormalities to be diagnosed in life by cross sectional echocardiography.

Case reports

PATIENT 1

A four year old girl was referred to our hospital with a diagnosis of congenitally corrected transposition of the great arteries, mild pulmonary stenosis, and left atrioventricular valve (tricuspid valve) regurgitation. She remained well until epigastric pain and hepatomegaly developed when she was 13 years old.

A transthoracic echocardiogram performed at that time confirmed the presence of the usual atrial arrangement, with discordant atrioventricular and ventriculoarterial connections. The only haemodynamically important additional finding was of severe obstruction of the left ventricular outflow tract related to an aneurysm of the mitral valve that had prolapsed into the subpulmonary region (fig 1A). Transoesophageal echocardiography confirmed the presence of a large aneurysm of the anterior leaflet of the mitral valve (fig 1B). Cardiac catheterisation showed a peak systolic gradient of 100 mm Hg across the left ventricular outflow tract and a large aneurysm of the mitral valve was seen prolapsing into the pulmonary outflow tract during ventriculography (fig 2).

PATIENT 2

An 18 year old man was referred for assessment of complex congenital heart disease. He had developed cyanosis in the neonatal period and underwent cardiac catheterisation in another institution, at which a diagnosis of usual atrial arrangement, absent right atrioventricular connection, and a discordant ventriculoarterial connection was formed. There was progressive pulmonary stenosis with reduced pulmonary blood flow and so a right Blalock-Taussig shunt was performed when he was six years old. He was admitted to this hospital aged 23 years with a view to planning further management.

Cross sectional echocardiography unexpectedly showed the usual atrial arrangement, a discordant atrioventricular connection, and a discordant ventriculoarterial connection. There was a large ventricular septal defect with subpulmonary and valvar pulmonary stenosis. The left ventricle was diminutive and colour Doppler echocardiography failed to identify any flow across the miniature mitral valve (fig 3). The patient subsequently had an uncomplicated Fontan operation (atriopulmonary anastomosis). At surgery a pinhole orifice was detected in the mitral valve; this was closed by direct suture.

Discussion

These patients show abnormalities of the morphological mitral valve in congenitally corrected transposition of the great arteries. We are not the first to show the presence of such abnormalities in this group of patients. They were also found in 55% of specimens studied at necropsy by Gerlis and co-workers.[1] It has been suggested, however, that such abnormalities tend to be minor and of doubtful surgical significance. The development of subpulmonary stenosis in patient 1, related to an aneurysm of the mitral valve, highlights the intimate relation between the pulmonary outflow tract and the atrioventricular valves in hearts with a discordant ventriculoarterial connection, which causes the pulmonary valve to be wedged between the mitral and tricuspid orifices.

The development of important obstruction of the pulmonary outflow tract is a common complication of congenitally corrected transposition of the great arteries, occurring in about 40% of patients.[2] This obstruction may be valvar, muscular or, more usually, related to aneurysms of the septal structures and tissue tags blocking the outflow tract. It is imperative

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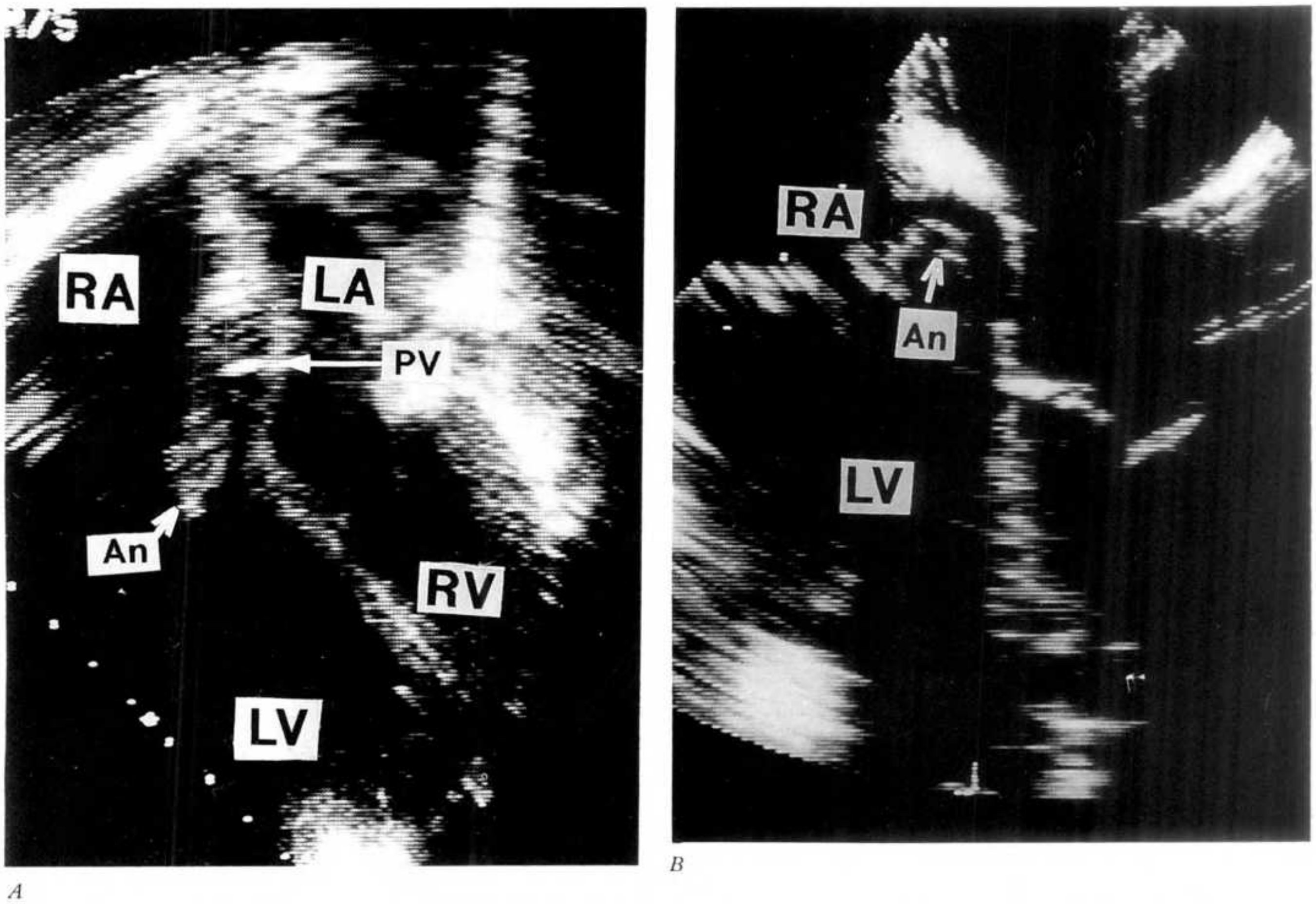

Figure 1 (*A*) *Transthoracic echocardiogram, taken during ventricular diastole, from an apical window in patient 1. There are discordant atrioventricular connections. The mitral and pulmonary valves* (*PV*) *are in fibrous continuity and there is an aneurysm on the mitral valve* (*An*). (*B*) *Transoesophageal echocardiogram in patient 1 during ventricular systole. The aneurysm on the mitral valve is prolapsing towards the pulmonary outflow tract. RA, right atrium; LA, left atrium; LV, left ventricle; RV, right ventricle.*

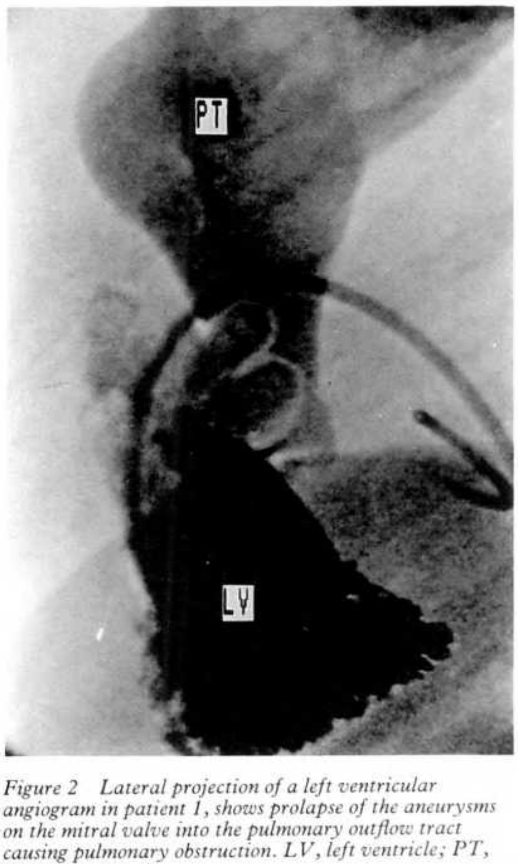

Figure 2 Lateral projection of a left ventricular angiogram in patient 1, shows prolapse of the aneurysms on the mitral valve into the pulmonary outflow tract causing pulmonary obstruction. LV, left ventricle; PT, pulmonary trunk.

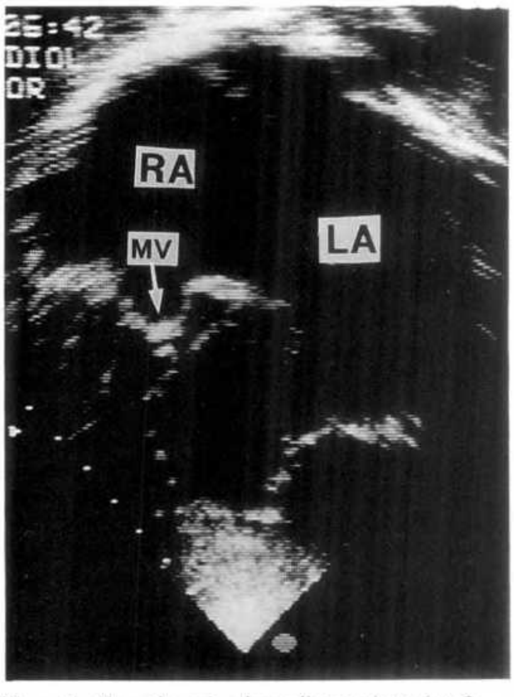

Figure 3 Transthoracic echocardiogram in patient 2 shows a miniaturised mitral valve (*MV*). *Although appearing imperforate, a patent but severely stenosed orifice was found at surgery. RA, right atrium; LA, left atrium.*

to identify accurately the origin of these aneurysms and tags when surgical resection is contemplated, because of the close relation between the atrioventricular conduction axis and the pulmonary outflow tract in this condition.[2] One pathological study showed that the source of these aneurysms and tags may be from the membranous septum, the tricuspid valve, or from the pulmonary valve itself, although this study did not identify a mitral valve origin in any case.[2]

Levy and co-workers showed subpulmonary obstruction related to abnormalities of the mitral valve in three patients studied at necropsy.[3] One of these patients was similar to ours, in that there was an intact ventricular septum and a 2 cm aneurysm of the anterior leaflet of the mitral valve, which prolapsed into the left ventricular outflow tract. To our knowledge, however, ours is the first antemortem report of this phenomenon. Interestingly, in retrospect, an echocardiogram performed on the patient of Levy and co-workers at the age of four years had shown an insignificant aneurysm of the mitral valve, thus highlighting the ability of this dynamic lesion to change its form and function with time.[1 4]

Patient 2 was originally diagnosed as having no right atrioventricular connection, a dominant left ventricle, and a discordant ventriculoarterial connection. It must be emphasised that this diagnosis was made before the introduction of cross sectional echocardiography. The subsequent recognition of a biventricular atrioventricular connection when he was seen in this hospital emphasises the need for careful transthoracic or transoesophageal echocardiograms in these patients. Clearly it had important surgical implications, as the development of regurgitation or diastolic right to left shunting through the miniature mitral valve after the Fontan operation may have had significant haemodynamic consequences.

In summary, clinically important abnormalities of the mitral valve may be present in patients with congenitally corrected transposition of the great arteries. These abnormalities may be readily identified by careful cross sectional echocardiography.

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CONCEPT

An analysis of the incidence of myocardial metastasis from solid cancers

Leonard Weiss

Abstract

Metastasis to the heart is compared with that to other target sites in terms of incidence, tissue susceptibility, and cancer cell injury within the microcirculation. At necropsy the myocardium is the sixth most common site for arterial metastasis among eight target organs in ten different types of disseminated primary cancer. However, the metastatic efficiency index (incidence/blood flow) indicates that the myocardium is no less susceptible to metastatis per unit of cancer cells delivered than most other sites examined. The analyses also indicate that cancer cells causing myocardial metastasis are mainly derived from metastatic or primary tumours in the lungs. Experiments on laboratory animals suggest that the failure to develop myocardial metastasis in 80 to 98% of patients with metastatic cancer is at least partially due to lethal, deformation-associated, mechanical damage inflicted on cancer cells trapped within the myocardial microvasculature.

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The aims of this paper are first to record and comment on the incidence of cardiac metastasis seen at necropsy in cases with a history of different, metastasing "solid" cancers. Second, this incidence will be compared with that of other target organs. Third, the susceptibility of the myocardium to haematogenous metastasis will be compared with that of other organs by use of metastatic efficiency indices. Finally, some mechanisms influencing the development of haematogenous metastasis in the myocardium will be discussed in the light of laboratory experiments.

Incidence of myocardial metastasis

Interest in myocardial metastasis has been limited because it is not usually diagnosed during life and when it is it is usually during the terminal phases of cancer. It is a truism that the actual numbers of cases detected are highest for the most common cancers; this is sometimes confused with the real incidence in each different type of primary cancer. In addition, in each type of primary cancer not only must a distinction be made between the incidence in patients with metastatic and non-metastatic disease but also attention must be given to the occurrence of metastatic "cascades", as discussed later.

True embolic metastasis to the myocardium occurs via the coronary arteries and, much less commonly, by implantation in the right cardiac chambers of cancer fragments carried in the venae cavae. In the present context it is important to discriminate between these lesions and non-metastatic extension from contiguous tumours, particularly of the bronchus and oesophagus and in the mediastinal lymph nodes.[1] According to Willis lymphatic permeation from the epi and peri cardial lymphatic vessels is not rare and the less common invasion of the vena cava and pulmonary veins extends no further than the atria by the time of death. The analyses made here will be confined to true embolic metastasis of the myocardium via the coronary arteries, with the less common routes or lesions excluded or ignored.

Table 1 Incidence (%) of metastasis from primary carcinomas in 10 target organs

	Percentage target organ involvement							
Metastatic primary cancers	*Kidneys*	*Brain*	*Bone*	*SM*	*Skin*	*Heart*	*Thyroid*	*Adrenals*
Breast	17·0	22·8	61·8	15·5	19·5	10·3	24·0	31·2
Colorectum	13·0	11·0	27·0	3·0	5·0	2·0	4·0	31·0
Oesophagus	36·8	13·2	28·9	7·9	0	13·4*	13·2	42·1
Kidney	21·2	19·4	10·2	3·5	5·3	14 0	10·6	20·1
"Lung"	22·5	42·9	32·5	—	<1·0	7·5	2·5	35·6
Lung/SCC	16·0	37·3	56·2	—	—	17·2*	4·6	35·0
Ovary	6·3	2·9	11·3	—	5 2	5·2	14·7	20·4
Pancreas	18·9	8·1	47·0	9·2	3·8	8·1	3·2	44·8
Prostate	14·2	2·1	66·8	—	2·6	3·0	2·1	17·3
Stomach	13·0	6·9	16·8	5·3	3·8	5·6*	2·3	3·5

SCC, small cell carcinoma; SM, skeletal muscle.
*Incidence of cardiac metastasis reference 2; sources for other sites given in reference 5.

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Table 1 shows the incidence of metastatis in the myocardium and other target organs from 10 common primary cancers when selective criteria indicated above are used. In addition, the incidence of myocardial metastasis in the cervix uteri, urinary bladder, and uterus was 6·1%, 11·8%, and 16·7% respectively.[2] These incidences are conservative because false negative reports are likely as a result of sampling and detection errors during necropsy[3] and subsequent standard histopathological examination of tissues.[4]

For carcinomas of the oesophagus, bronchus (small cell carcinoma), and stomach data from the Klatt and Heitz[2] series were used because previously collected data on target sites for these primary cancers did not include the incidence of cardiac metastasis. The inclusion of data from this series was justified because the incidences of cardiac metastasis reported by Klatt and Heitz in primary metastatic cancers of the breast (12·5%), colorectum (3·1%), kidney (11·5%), and ovary (7·7%) were very close to the corresponding values obtained from other sources[5] and given in table 1.

Data on the 13 specified types of primary cancer were available for up to eight target sites—that is for a total of 99 of a possible maximum of 104. For the eight tabulated sites cardiac metastases had the sixth mean highest incidence (table 1). Among those primary cancers with cardiac metastases, the highest incidences occurred in cases with a history of small cell carcinoma of the lung (17·2%) and carcinomas of the uterus (16·7%), kidney (14%), and oesophagus (13·4%). The high incidence in uterine and kidney carcinoma could not have been the result of direct extension from these primary lesions. Conversely, the similar incidences at these sites and in the lung and oesophagus, suggests that extension from these latter primary sites played a minor role in the genesis of cardiac metastasis, as recorded here.

Cardiac metastasis was present in 9·3% of approximately 2500 cases with a history of metastatic primary cancers. This mean value compares with that of 14·9% (range 7–26%) in the 1934 cases collated previously,[6] which also showed that in the absence of detectable metastases elsewhere, particularly in the lungs, myocardial metastatis was rare. For example, necropsies performed in the Roswell Park Cancer Institute from 1959 to 1982, on 9501 patients with histories of primary cancers (excluding the lung) showed a 19% incidence of cardiac metastasis in 4330 patients with lung metastasis; however, among 5109 patients without detected lung metastases only 2·7% had cardiac metastasis.[6] This can be accounted for by traffic of cancer cells to the myocardium. Only a small proportion of cancer cells shed by primary lesions are expected to survive passage through the microcirculation of the lungs where most are trapped and, of these, most are killed.[7,8] In the case of cancer cells entering the portal system from colorectal carcinomas for example, even fewer will survive direct passage through the microvasculature of both the liver and lungs en route to the myocardium, where most of the delivered cells are also killed. This suggestion is supported by the low (2%) incidence of myocardial metastasis in colorectal carcinoma. One mechanism for rapid cancer cell death within the microvasculature is discussed below (section 3).

In view of the massive intravascular death of cancer cells the commonest way for large numbers of tumourigenic cancer cells to enter the myocardium via the coronary arteries is directly from lung tumours (primary and metastatic lesions) via the pulmonary veins. This at least partially accounts for the higher incidence of myocardial metastasis in patients with pulmonary metastasis over those without them and for the higher incidence in patients with primary small cell carcinomas of the lungs. This process of metachronous seeding by metastasis from metastases (metastatic "cascades") was shown in various cancers by Bross *et al*[9] and in colonic,[10] renal,[11] and pancreatic[12] carcinomas.

Metastatic patterns and metastatic efficiency indices

Two non-exclusive explanations have been offered for the specific patterns of target organ involvement seen with different primary cancers. In the first[13] the dominant factor is considered to be the numbers of cancer cells

Table 2 Metastatic efficiency indices (MEI): percentage of target organ involvement (from table 1) divided by target organ blood flow

	Target organs							
	Blood flow (ml/min)							
Metastatic primary cancer	*Kidneys (1000)*	*Brain (750)*	*Bone (600)*	*SM (560)*	*Skin (400)*	*Heart (240)*	*Thyroid (100)*	*Adrenals (90)*
Breast	0·017	0·030	0·103	0·028	0·049	0·043	0·240	0·347
Colorectum	0 013	0·015	0·045	0·005	0·013	0·008	0·040	0·344
Oesopahgus	0·037	0·018	0·048	0·014	0	0·056	0·132	0·468
Kidney	0·042	0·026	0·017	0·006	0·010	0·058	0·110	0·447
"Lungs"	0·023	0·057	0·054	—	0·001	0·031	0·025	0·396
Lungs/SCC	0·016	0·050	0·094	—	0 001	0·072	0·046	0·389
Ovary	0·006	0·004	0·019	—	0·013	0·022	0·147	0·229
Pancreas	0·019	0·011	0·078	0·016	0·010	0·034	0·032	0·487
Prostate	0·014	0·003	0·111	—	0·007	0 013	0·021	0·192
Stomach	0·013	0·009	0·028	0·009	0·010	0·023	0·023	0·039

*Red bone marrow. Numbers in parentheses are organ blood flows in ml/min.

delivered in the bloodstream to the different target sites. Thus the lungs are the most common early sites for primary cancers with initial drainage into systemic veins and the liver is the most common for those draining into the portal system.

In mice the delivery of cancer cells to different target organs after they had been injected into the left ventricular cavity correlated closely (r = 0·99) with target organ blood flow.[14] In humans delivery of cancer cells is also expected to correlate with blood flow. I have collated information from various sources[15] and table 2 includes information on myocardial blood flow.[16 17]

A comparison of the incidence of metastases in the different target organs (table 1) with their blood flow (table 2) does not show a correlation. In addition, only in the case of colorectal carcinoma does the incidence of cardiac metastasis lie between the values for the skin and thyroid, which have blood flows respectively above and below that in the myocardium. Therefore, although the delivery of cancer cells to target organs is an absolute requirement for metastasis, it does not account for the incidence patterns recorded here. However, the only data available on incidence relate only to whether or not evidence of metastasis was detected in any site, not how many metastases were present.

The disparity between cancer cell delivery and blood flow is addressed by the "seed-and-soil" hypothesis of Paget.[18] In this, differential interactions between different sites ("soils") and different types of cancer cells ("seeds") are thought to determine the relative susceptibilities of target sites to metastasis.

To discriminate between the differential delivery of cancer cells and differential interactions with target sites after delivery a semi-quantitative metastatic efficiency index (MEI) (percentage incidence of organ involvement divided by organ blood flow (ml/min) was developed.[5] In the initial study of the involvement of eight different target sites by metastasis from 19 groups of primary cancers, the MEIs that could be calculated in 135 of 152 possible situations, fell into three decades. Most (65%) had values of 0·01–0·09, 20% had values of 0·1–0·9 (indicating a "friendly" microenvironment with a relatively high incidence of metastasis per unit number of delivered cancer cells), and in contrast 15% had MEIs of 0–0·009 (indicating a "hostile" environment with a relatively low incidence of metastasis per delivered unit).

Table 2 shows the MEIs calculated for 76 of 80 possible combinations of primary and target sites: 48 (63%) fell into the middle decade, which included all cases of cardiac metastasis. The mean (SEM) MEI for these lesions was 0·039 (0·006), including metastasis from primary cancers of the cervix uteri (0·025), bladder (0·049), and uterus (0·070). Therefore, although the incidence of myocardial metastasis was sixth in the hierarchy of the eight target sites reported, on the basis of MEI only 16 (20%) of 76 of other sites fell into the higher susceptibility decade and, of these, most were in the adrenals and thyroid.

Death of cancer cells in the myocardial microcirculation

Among those patients dying with metastatic cancer in the present study, between 83 and 98% did not have cardiac metastases detectable at necropsy. Large numbers of cancer cells must have been delivered to the myocardium but most of them must have failed to grow into metastases. This is an example of metastatic inefficiency.[8]

Interactions of cancer cells with the microvasculature of target sites are thought to be important rate regulators of haematogenous metastasis.[19] Studies in laboratory animals[20] showed that most cancer cells delivered to the myocardium via the coronary arteries after left ventricular injection are killed within several minutes: virtually no cancer cells were detected on histochemical examinations, and sensitive myocardial bioassays indicated that between 80% and 95% of cells entering the myocardium were rapidly killed. Cancer cell death was not due to the toxicity of the myocardium *per se*. Fewer cancer cells were killed when they were added to minced myocardium, which indicates that toxicity of the myocardium alone did not explain cancer cell killing.

One mechanism accounting for the destruction of cancer cells in the microvasculature of the heart and other target organs comes from considerations of cell geometry.[6 21] In vessels down to arteriolar diameter, circulating cancer cells tend to remain spherical. But when they enter vessels that have smaller diameters than they do they become cylindrical. Because a sphere has the smallest surface area of any body of equal volume, this transformation from sphere to cylinder must be associated with an increase in the surface area of the cancer cells. This increase can be apparent and be accomplished by non-lethal surface unfolding or, if unfolding is insufficient to meet the geometric demands, the increase may be real and accomplished by stretching of the surface membranes of the cancer cells. Biological membranes in general cannot be stretched to increase their surface areas by more than 4%, before the tension within them rises to the critical level for rupture, with consequent cell death. Intravascular cancer cell deformation with increases in surface area and death has been directly demonstrated by vital microscopy and has been shown to be the result of mechanically induced deformation.[22] Small cells with a high degree of membrane rugosity are expected to be most resistant to membrane damage induced by intravascular deformation. Thus erythrocytes and leukocytes, which are small and have membrane "excess", are more resistant than the generally larger and often less rugose cancer cells from solid tumours. Some leukaemia cells fall between these two extremes. It is therefore of interest that cardiac metastasis is more common in patients with lymphoreticular malignancies[23–25] than in those with solid tumours.

The myocardial capillaries would be expected to be especially lethal to cancer cells because of the external pressures acting on them during systole. The lethal effects of additional pressure on cancer cells with partially unfolded surface membranes has been demonstrated in vitro.[26] Although measurement of intramyocardial pressure is technically difficult and interpretation is controversial,[27] it is generally agreed that systole causes pressure gradients across the myocardium, decreasing from endocardium to epicardium.[28] These pressures correspond to hoop tensions in the muscle fibres that are greater than 2×10^5 dyn/cm,[29] and although the details of mechanical coupling between the myocardium, capillaries, and cancer cells are not known, these tensions are four to five orders of magnitude higher than the critical tensions required to rupture cancer cell membranes.[20] The fact that the MEIs for the myocardium were in the middle decade, however, suggests that in some target organs other factors have similar numerical effects to those of myocardial contraction. Direct evidence that muscle contraction is associated with increased killing of cancer cells trapped in the microvasculature, comes from bioassays of cancer cells delivered to contracting, resting, and paralysed quadriceps muscles in mice[30]: also the MEIs for skeletal muscle (table 2) are in the middle and low decades.

In the face of the mechanical damage outlined above it is at first sight surprising that myocardial metastases develop at all: none the less, even an inefficient process will succeed if repeated often enough. One possible additional explanation is that metastases develop initially at the myocardial surfaces where compression is minimal; clumps of cancer cells are more likely than single cells to be arrested in superficial vessels, which have larger diameters than the deeper vessels. Subsequent invasion associated with histolysis from the metastasis/heart interface could then provide a pressure-relief mechanism for the subsequent successful invasion and growth of metastases into the myocardium. Some support for this suggestion comes from Klatt and Heitz's[2] observation that in 110 cases with cardiac metastasis, there were 100 surface lesions (83 epicardial and 17 endocardial) compared with 42 intramyocardial lesions.

It must be emphasised that deformation-induced, lethal damage of cancer cells in the microvasculature is only one of several rate regulators of metastasis.[8,19]

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PRACTICE REVIEWED

Conservative surgery of the mitral valve: a report of the first 100 cases from one unit and one surgeon

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Abstract

***Objective*—To report the first 100 mitral valve repairs performed in a unit with an aggressive approach to conservative mitral valve surgery.**

***Design*—Case notes were reviewed retrospectively and patients invited for clinical examination and cross sectional and Doppler echocardiography.**

***Setting*—Tertiary cardiothoracic referral centre.**

***Patients*—Between December 1985 and April 1991 mitral valve repair was carried out on 100 patients (66 males). Patients with pure mitral stenosis were excluded. Sixty seven had degenerative and 15 rheumatic mitral valve disease. Median age was 66 (range 12 to 79) years, with an interquartile range of 59 to 71 years.**

***Interventions*—Operative procedures included annuloplasty ring in 97, resection of the posterior leaflet in 67, resection of endocarditic portion of posterior leaflet in four, commissurotomy in six, and correction of anterior leaflet abnormalities in seven. Thirty nine concomitant cardiac procedures were performed in 32 patients. Six operations were emergencies, and three of these required concomitant procedures.**

***Main outcome measures*—Mortality, operative failure rate, patients' functional state and degree of residual mitral regurgitation, incidence of thromboembolism, and endocarditis.**

***Results*—Follow up ranged from one to 59 months, median 14 months, and an interquartile range of four to 23·5 months. Early mortality was 1%, late mortality 5%, and there was a 2% reoperation rate. Eighty four patients had moderate to severe mitral regurgitation preoperatively. At follow up mitral regurgitation was absent or mild in 78. Eighty six patients were in New York Heart Association (NYHA) class I–II at follow up compared with 80 in NYHA class III–IV preoperatively. There were no thromboembolic events.**

***Conclusion*—This study shows that satisfactory results can be obtained with mitral valve repair in a fairly elderly population with a high incidence of concomitant cardiac disorders. We suggest that these encouraging results will lead to earlier mitral valve repair in mitral regurgitation.**

(*Br Heart J* 1992;**68**:505–9)

Reconstructive mitral valve surgery for mitral regurgitation was first described in 1957.[1 2] In the United States and Europe, however, mitral valve replacement has, until recently, been the standard operation for mitral regurgitation after the first successful mitral prosthetic valve implantation in 1961.[3] Some European centres continued to favour mitral valve reconstruction, with Carpentier's group pioneering techniques of repair based on functional analysis of the mitral valve.[4] The satisfactory late results from these centres has stimulated a wider interest in repair techniques in recent years.[5 6] Mitral valve repair techniques are complex and the well described associated learning curve has deterred many surgeons and cardiologists from developing a service.[7 8] We review our early experience with 100 mitral valve repairs performed by one surgeon between December 1985 and April 1991.

Patients and methods

PATIENTS

Mitral valve repair for mitral regurgitation was started in our institution in December 1985 and during the period to April 1991, 100 patients underwent Carpentier techniques of mitral valve repair by one surgeon. Ninety four patients had pure mitral regurgitation and six had mixed mitral valve disease. Patients with pure mitral stenosis were excluded from the study. Sixty six were male and 34 were female. Median age was 66 (range 12 to 79) years with an interquartile range of 59 to 71 years. This represents a more elderly population than in most reported series. Our use of mitral valve reconstruction has increased each year as experience with the technique was gained (fig 1). Table 1 lists the causes of mitral regurgitation in our patients.

Preoperative New York Heart Association

Figure 1 Mitral valve repair v replacement over the period 1985–1991 (four months only for 1991).

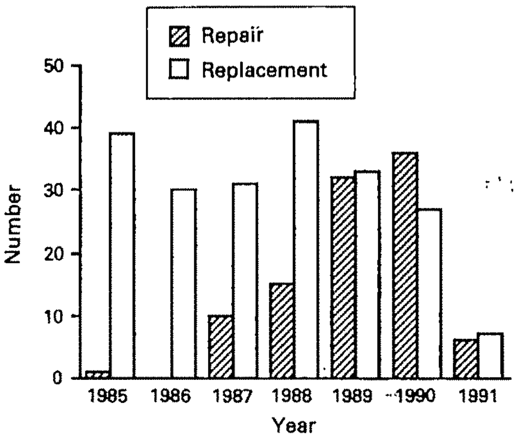


Table 2 Functional classification of valve dysfunction and underlying anatomical lesions (sum of lesions > number of patients due to associated lesions

Valve dysfunction		*No of patients*
Type 1 Normal leaflet motion:		20
Annular dilatation/deformation		18
Leaflet perforation		2
Type 2 Leaflet prolapse:		74
Prolapse PL		70
Chordal rupture	60	
Chordal elongation	3	
Intact chordae	6	
Ruptured papillary muscle	1	
Prolapse AL		2
Chordal rupture	1	
Ruptured papillary muscle	1	
Prolapse AL and PL		2
Chordal elongation	1	
Chordal rupture	1	
Type 3 Restricted leaflet motion:		6
Commissural fusion	6	
Chordal fusion		
PL	1	
AL	1	

PL, posterior leaflet; AL, anterior leaflet.

(NYHA) functional classification was ascertained by examination of the patients' records. Ninety per cent of patients underwent preoperative, and all patients postoperative cross sectional and Doppler echocardiography to determine the severity of mitral regurgitation. The severity of mitral regurgitation was assessed by cardiac catheterisation in the 10 patients who did not have preoperative echocardiography.

At follow up, NYHA classification, clinical examination, cross sectional and Doppler echocardiogram to determine mitral valve area, degree of mitral regurgitation, and left atrial size were assessed. Mitral regurgitation was graded by pulsed Doppler assessment of the depth of jet into the left atrium and intensity of the regurgitant signal, with the scoring system described by Pons-Llado *et al.*[9] This is a sensitive method of detecting and assessing the severity of mitral regurgitation.

Table 1 Causes of mitral regurgitation

Aetiology of valve lesions	*No of patients*
Degenerative	67
Rheumatic	15
Ischaemic	7
Endocarditis	8
Congenital	1
Functional	1
Infiltrative	1

METHODS

Intraoperative examination of the mitral valve allowed classification of patients according to Carpentier's three functional categories based on leaflet function—namely, normal leaflet motion, prolapsed leaflet, and restricted leaflet motion.[4] Table 2 summarises the functional type of mitral valve dysfunction and the underlying anatomical lesions.

Type 1 mitral regurgitation was treated with a prosthetic ring annuloplasty. Mitral regurgitation associated with increased leaflet mobility was treated by leaflet resection, chordal shortening, or chordal transposition. In type 3 disease increased leaflet mobility was attained by commissurotomy, chordal division, chordal excision, and division of the papillary muscles. In type 2 and 3 mitral regurgitation a prosthetic remodelling ring annuloplasty was usually required. Ninety seven patients were treated with a prosthetic ring annuloplasty. Seven patients had abnormalities of the anterior leaflet corrected.

Thirty nine concomitant cardiac procedures were performed in 32 patients. In patients undergoing concomitant coronary artery bypass grafting (CABG) a mean of two grafts, range one to three, were performed. Six patients were operated on as emergencies; five of these were over 65 years old and three had concomitant cardiac procedures, CABG in one and aortic valve replacement (AVR) in two. Eighteen patients in total underwent CABG, 15 of these patients were over 65 years old and represented a high risk subgroup. Tables 3 and 4 list details of the surgical procedures and associated cardiac procedures performed. Anticoagulation with warfarin was used for three months only in those patients in sinus rhythm, to allow endothelialisation of the ring, but continued indefinitely in patients with persistent atrial fibrillation or mechanical aortic valve prosthesis.

Eight patients with endocarditis underwent mitral valve repair and these represent an interesting subgroup. Two patients had perforation of the anterior leaflet repaired by oversewing in one and patch repair in the second. Four patients underwent resection of the endocarditic portion of the posterior leaflet and an annuloplasty ring was inserted in three. In the remaining two patients the endocarditis had healed and a quadrangular resection of the posterior leaflet and ring annuloplasty were performed.

Table 3 Operation details

Operative procedures		*No of patients*
Prosthetic ring annuloplasty		97
Carpentier	93	
Sliding annuloplasty (Carpentier)	1	
Duran-Medtronics flexible ring	3	
PL Resection		71
Quadrangular resection	66	
Double resection	1	
Resection endocarditic portion	4	
Chordal shortening AL		2
Reattachment of chordae to AL		1
Transposition of chordae		
PL		1
AL		1
Patch repair AL		2
Commissurotomy		6
Division of papillary muscles		3
Chordal division		
PL		1
AL		1
Excision of chordae		2

PL, posterior leaflet; AL, anterior leaflet.

Table 4 Cardiac procedures concomitant with mitral valve repair

Concomitant procedures	*No*
CABG	18
AVR	12
ASD Repair	1
Tricuspid annuloplasty	4
Tricuspid valvotomy	1
Aortic annulus decalcification	1
Posterior annulus decalcification	3
Enlargement of aortic root	1
Replacement of aortic root	1

CABG, coronary artery bypass grafts; AVR, aortic valve replacement; ASD, atrial septal defect.

Results

Ninety three of the 100 patients in this series were reviewed; six had died and one had undergone reoperation and valve replacement. Follow up ranged from one to 59 months, median 14 months, with an interquartile range of four to 23·5 months.

MORTALITY

One hospital death occurred in a patient with amyloid infiltrative cardiomyopathy as part of extensive systemic amyloidosis shown at post mortem examination. This had been undiagnosed preoperatively and may therefore have been an inappropriate referral for mitral valve repair.

There were five late deaths, three of which were not valve related. Table 5 summarises clinical details and causes of death of the patients who died.

REOPERATION

Two patients required reoperation, in one at seven months after repair it was found at reoperation that the original repair was intact but that there was fresh chordal rupture to the anterior leaflet. The second patient underwent reoperation and mitral valve replacement for prosthetic ring dehiscence and paraprosthetic leak detected at the routine follow up examination performed for this study.

ANTICOAGULANT RELATED HAEMORRHAGE

One patient on long-term warfarin treatment for an associated mechanical aortic valve prosthesis died from intracerebral haemorrhage when undergoing treatment for bacterial endocarditis (table 5). A second patient developed a haemorrhagic cerebrovascular accident one week after repair and has a residual dense left hemiplegia.

THROMBOEMBOLISM

There were no documented thromboembolic events reported in this series.

ENDOCARDITIS

Two patients died after developing new bacterial endocarditis after operation (table 5). One patient, already mentioned, had an associated mechanical aortic valve prosthesis, presented with bacterial endocarditis four months after operation, and died from an intracerebral haemorrhage. The second patient developed endocarditis at two months after repair.

FUNCTIONAL STATE OF PATIENTS AND DOPPLER ECHOCARDIOGRAPHY

Mitral regurgitation was graded as severe or moderate to severe in 84 patients before operation; at follow up mitral regurgitation was absent to trivial or mild in 78. Eighty patients were in NYHA class III–IV before operation compared with 86 patients in NYHA class I–II after mitral valve repair. All but four patients had improved by at least one NYHA class. Figure 2 graphically shows the improvement in mitral regurgitation and patient functional state after operation.

At follow up six patients were in NYHA class III and echocardiography showed poor global left ventricular function with trivial to mild mitral regurgitation. Three of these patients had poor left ventricular function before operation, three had been in NYHA class IV, and three in NYHA class III.

One patient had moderate to severe mitral regurgitation as a result of ring dehiscence and paraprosthetic leak. Valve replacement was required. Eight patients were noted to have moderate transvalvar mitral regurgitation and one had apparent paraprosthetic regurgitation. All of these patients were symptomatically well, with six in NYHA functional class I and two in NYHA class II.

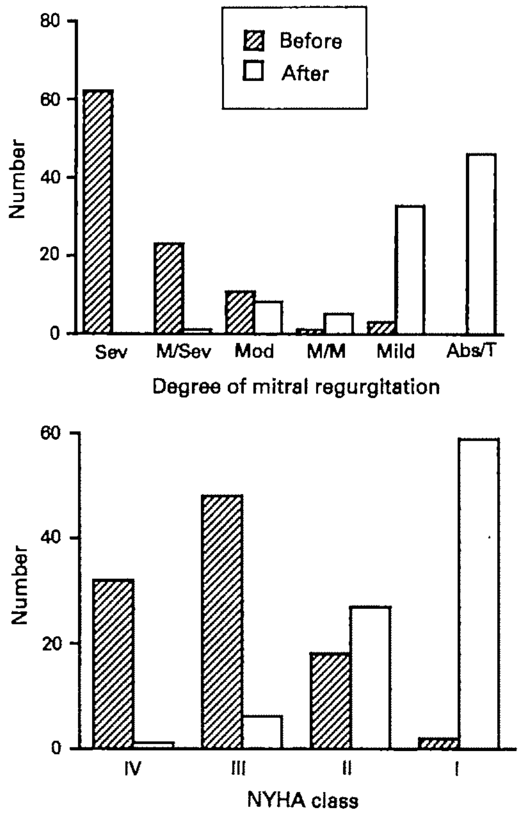
We noted paradoxical or impaired septal motion on echocardiography in all but two

Table 5 Clinical details of valve and non-valve related mortality*

Cause of death	*Sex*	*Age*	*Months after operation*	*Aetiology of MVD*	*Procedures*	*NYHA class before operation*	*Mitral regurgitation before operation*
Cerebral* haemorrhage (on warfarin)	M	51	4	Rheumatic	Ring AVR	I	Mild to moderate
Endocarditis*	M	73	2	Degenerative	PL resection of ring	IV	Severe
Myocardial infarct	W	72	4	Degenerative	PL resection of ring CABG	IV	Severe
Myocardial failure	M	68	2	Rheumatic	Ring AVR	IV	Mild to moderate
Myocardial failure	M	69	2	Degenerative	PL resection of ring	III	Severe
Left ventricular failure (amyloid)	W	59	1 Day	Infiltrative	Ring	III	Moderate

Footnotes as for table 4. MVD, mitral valve disease; PL, posterior leaflet.

Figure 2 Mitral regurgitation and NYHA classification before and after valve repair. Sev, severe; M/Sev, moderate to severe; Mod, moderate; M/M, mild to moderate; Abs/T, absent or trivial.



patients and this was unrelated to the type of annuloplasty ring used. This finding is unexplained and to the best of our knowledge not reported in other series of mitral valve repairs.

Discussion

The now well recognised limitations of prosthetic and bioprosthetic valves have stimulated a renewed interest in techniques of mitral valve repair.

Mitral valve repair has been shown to be durable[5,6] and valve related complications are low.[5,10,11] Preservation of the mitral valve, with intact subvalvar apparatus (chordae tendineae and papillary muscles) has been shown in the laboratory and clinically to preserve left ventricular function.[12,13] There have been no randomised trials comparing mitral valve repair and replacement in mitral regurgitation; however, several comparative case matched studies report improved survival with mitral valve repair.[10,14,15]

Mitral valve replacement in acute ischaemic mitral regurgitation has a poor prognosis with hospital mortalities reported as high as 45%.[16] Rankin *et al* and Hickey *et al* reported improved operative survival after mitral repair rather than replacement in ischaemic mitral regurgitation.[17,18] Likewise Kay *et al* showed improved long and short-term survival especially in patients with reduced ejection fraction.[19]

There is evidence, therefore, that conservation of the mitral valve has advantages over valve replacement and is now accepted by many as the operation of choice, when possible, in mitral valve disease.

We had one (1%) hospital death in this series compared with 1·5% to 8·5% reported in other series with similarly aged patient populations.[7,11,20–22] The late mortality of 5% in this medium term follow up also compares favourably with other series of similar follow up.[21–23]

The reoperation rate of 2%, similar to that experienced by Cosgrove *et al*,[7] shows that the learning curve in this series was not problematical and superior to rates of 7% and 8% in other series with similar population groups and follow up periods.[21,23] There have been no reports of thromboembolic events in our series and it is well accepted that thromboembolism is much lower than with mitral valve replacement. Obstruction of the left ventricular outflow tract due to systolic anterior motion of the mitral valve has been reported after mitral valve repair[24,25] but was not detected in this series. The occurrence of new endocarditis after reconstruction in two patients is similar to that experienced by Cohn *et al* but higher than in most reported series where the incidence of late endocarditis approaches zero.[21] This is lower, however, than the 3% to 6% incidence of late endocarditis after mitral valve replacement.[26,27]

There was no recurrence of endocarditis in the eight patients who underwent repair for mitral regurgitation secondary to mitral valve endocarditis.

Of the five symptomatic patients with poor left ventricular function and no evidence of mitral valve dysfunction, three had evidence of left ventricular dysfunction before operation and earlier intervention may have prevented the development of irreversible left ventricular damage.

Our early experience of mitral valve repair techniques has shown that satisfactory results can be obtained even in elderly high risk groups. We would hope that these encouraging results will lead to earlier mitral valve repair in mitral regurgitation, before the start of irreversible left ventricular failure.

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MEASUREMENT

Transoesophageal Doppler echocardiographic measurement of cardiac output by the mitral annulus method

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Abstract

***Objective*—To compare cardiac output measured by the transoesophageal Doppler and thermodilution techniques.**

***Design*—Prospective direct comparison of paired measurements by both techniques in each patient.**

***Setting*—Intensive care unit in a cardiovascular centre.**

***Patients*—65 patients after open heart surgery (mean (SD) age 53 (12) years).**

***Interventions*—Cardiac output was measured simultaneously by the transoesophageal Doppler and thermodilution techniques. Cardiac output was measured again after a mechanical intervention or volume loading.**

***Results*—The limits of agreement were $-2·53$ to $+0·83$ $l·min^{-1}$ for cardiac output measured by the Doppler and thermodilution techniques. This suggests that the Doppler method alone would not be suitable for clinical use. The second measurement of cardiac output by thermodilution was compared with cardiac output estimated from the first and second Doppler measurements and the first thermodilution measurement. The limits of agreement ($-0·55$ to $+0·51$ $l·min^{-1}$) were good enough for clinical use.**

***Conclusions*—After cardiac output had been measured simultaneously by both the Doppler and thermodilution techniques, subsequent transoesophageal Doppler alone gave a clinically useful measurement of cardiac output.**

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The Fick, dye dilution, and thermodilution methods are regarded as the most accurate methods for measuring cardiac output. Quantitative transthoracic Doppler echocardiography is used in many centres to measure cardiac output.[1] The transthoracic approach is known to be a valid method of measuring flow in the ascending aorta (suprasternal view), flow in the pulmonary artery (parasternal view),[2] left ventricular outflow (apical view),[3] and transmitral flow (apical view).[3]

Transoesophageal echocardiography has been used to monitor left ventricular performance[4] and diagnose myocardial ischaemia.[5] Transoesophageal systems can be used to obtain pulsed Doppler echocardiographic measurements, which permit determination of flow velocity in a specified location over time. Ultrasonic access to the heart from the oesophagus is not restricted by the lungs or ribs and the technique can be used to record blood velocity in patients after open heart surgery.

We used transoesophageal pulsed Doppler echocardiography to measure cardiac output from the transmitral flow velocity and the diameter of the mitral annulus.

Patients and methods

PATIENTS

We studied 65 patients (40 men and 25 women, aged (mean (SD)) 53 (12) years). Thirty seven patients underwent coronary artery bypass grafting, 15 aortic valve replacement, 12 reconstruction of the ascending aorta and/or aortic arch by composite valve graft or graft only, and one tricuspid valvuloplasty. All patients were postoperatively ventilated in the intensive care unit. Patients were sedated during ventilation. All patients were studied 1–48 h after operation in a stable haemodynamic condition. None of the patients showed clinical, echocardiographic, or Doppler evidence of mitral stenosis. None had mitral regurgitation of >1+ on preoperative left ventriculography (Sellers criteria)[6] or on pre and post operative pulsed Doppler echocardiography.[7] In all but the one who underwent tricuspid valvuloplasty the maximal distance from the tricuspid orifice reached by the regurgitant signals was less than 1·5 cm (+1 tricuspid regurgitation)[8] on pre and post operative transthoracic pulsed Doppler echocardiography. In one patient who had had severe tricuspid regurgitation and had had tricuspid valvuloplasty, postoperative transoesophageal Doppler echocardiography showed trivial tricuspid regurgitation, and transthoracic echocardiography performed 14 days after the operation confirmed +1 tricuspid regurgitation. All patients were in normal sinus rhythm. After an explanation of the nature and the purpose of the study they gave their informed consent.

CARDIAC OUTPUT DETERMINED BY TRANSOESOPHAGEAL DOPPLER ECHOCARDIOGRAPHY

All of the transoesophageal echocardiographic studies were performed a few minutes before cardiac output was measured by the thermodilution technique. A 3·75 MHz transoesophageal echocardiographic probe (Machida, ESB-37SR, Japan) was inserted into the oesophagus. Images were obtained with a directional pulsed Doppler flowmeter incorporated in a wide angle phased array echograph (Toshiba Sonolayergraph 65A and Toshiba SDS21A, Tokyo, Japan). This system uses a fast Fourier transformation by a spectral analyser system which displays the different red blood cell velocities within the cardiac chambers. The cut-off frequency of the high-pass filter was set to 400 Hz. The pulse repetition rate was 4 or 6 kHz. The depth of sample volume was about 3 mm. The smallest feasible angle was maintained during all Doppler measurements. Correction for the angle of incidence was made in all measurements. The angle of incidence was less than 20° in 27 patients and it ranged from 20° to 35° in 38. The Doppler signals were displayed simultaneously with the electrocardiogram and M mode echocardiogram by a strip chart recorder (Toshiba LSR20A) and a paper speed of 50 mm/s. Flow velocity components toward and away from the transducer were displayed above and below the baseline, respectively.

The transducer was manipulated to obtain a four chamber view with the sample volume at the centre of the mitral ring where the velocity was fastest. Colour flow imaging was used to keep the beam parallel with the transmitral flow. Mitral inflow velocity was recorded over several cardiac cycles. We used the machine's computer to obtain an integrated angle correction for the Doppler technique and then we used planimetry of the resulting mitral flow velocity curve to obtain the velocity-time integral for mitral flow (figure 1). Five beats were averaged for each determination.

The diameter of the mitral valve annulus was measured at the time of peak rapid filling flow velocity (fig 1). Measurements from a minimum of five cardiac cycles were averaged and the cross section area of the annulus was derived as $\pi \times r^2$, where r is half of the diameter of the annulus. This method assumes that the mitral annulus is circular and the cross sectional area is constant throughout diastole. Cardiac output was calculated as the product of the velocity-time integral for mitral diastolic flow and the cross sectional area of the mitral annulus (which gave the stroke volume) multiplied by heart rate. We called cardiac output determined by this Doppler technique the Doppler cardiac output.

A second independent observer repeated the Doppler determination of cardiac output in 15 patients to test for interobserver differences. Cardiac output measured by the Doppler technique was repeated a few minutes later in 15 patients to test for intraobserver differences. Inter and intra observer differences were determined as the difference between the two observations divided by the mean of the two observations.

CARDIAC OUTPUT MEASURED BY THE THERMODILUTION TECHNIQUE

A Swan-Ganz thermodilution catheter (American Edwards Laboratory) was inserted into the pulmonary artery. Cardiac output was determined by Swan-Ganz catheter with 5% glucose in water at 0°C as the indicator. We used a bedside thermodilution cardiac output computer (American Edwards Labratory, COC-9520-A) for the calculations. We called cardiac output determined by thermodilution the thermal cardiac output. Five measurements of thermal cardiac output were obtained. The high and low values were discarded and a mean of the three remaining values was calculated if the variability of these determinations did not exceed 15%. Because of considerable variability in 12 patients, five new measurements were made and the procedure

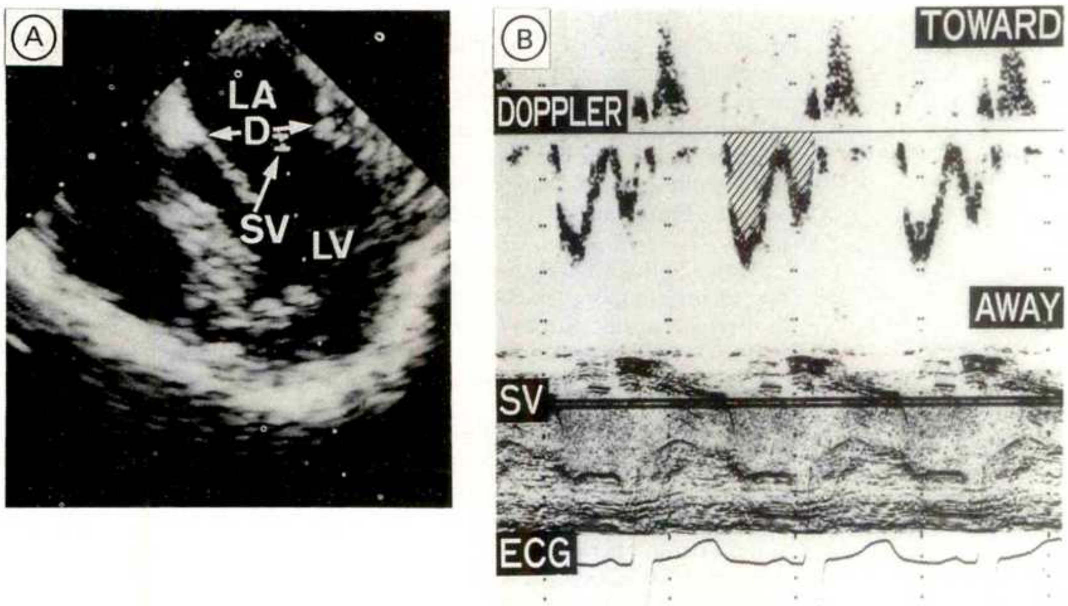

Figure 1 (A) Measurements of indices from mitral flow pattern. Transoesophageal four chamber view showing sampling volume (SV) for Doppler measurement (white arrow) in the centre of the mitral ring and the diameter (D) of the mitral valve annulus. (B) Doppler echocardiographic flow signal recorded at SV. Doppler flow signals indicate the instantaneous mean mitral flow velocity and are used to measure the mitral flow integral. LV, left ventricle; LA, left atrium; ECG, electrocardiogram; TOWARD, flow components toward the transducer; AWAY, flow components away from the transducer.

was repeated. To test inter and intraobserver variability, measurements of thermal cardiac output were repeated in 15 and 20 patients respectively. Inter and intraobserver differences were calculated as the difference between the two observations divided by the mean value of the two observations.

ESTIMATION OF THE SECOND MEASUREMENT OF THERMAL CARDIAC OUTPUT FROM THE FIRST AND SECOND MEASUREMENTS OF DOPPLER CARDIAC OUTPUT AND THE FIRST MEASUREMENT OF THERMAL CARDIAC OUTPUT

We measured changes in thermal cardiac output and Doppler cardiac output induced by fluid infusions or associated with positive end expiratory pressure or intraaortic balloon pumping.

Percentage changes in Doppler cardiac output were compared with those in thermal cardiac output. We also estimated what the second measurement (after intervention) of thermal cardiac output was from the first thermal cardiac output, first Doppler cardiac output, and the second Doppler cardiac output:

$$\text{Second thermal Doppler cardiac output (l/min)} = \text{first thermal cardiac output} \times \frac{\text{second Doppler cardiac output}}{\text{first Doppler cardiac output}}$$

We assessed whether the second thermal Doppler cardiac output was clinically valuable.

STATISTICAL ANALYSIS

Data are expressed as mean (SD). Data were analysed by the method of Bland and Altman.[9]

Results

Table 1 gives the measurements in individual patients. No patients were excluded from the study because of poor quality echocardiographic or Doppler data.

ASSESSMENT OF THERMAL CARDIAC OUTPUT AND DOPPLER CARDIAC OUTPUT BY THE METHOD OF BLAND AND ALTMAN

Table 2 lists the results of this statistical analysis. A plot of the difference between Doppler cardiac output and thermal cardiac output compared with the average of these two measurements (fig 2) showed that Doppler cardiac output can be 2·53 l/min less than or 0·83 l/min greater than the thermal cardiac output. This is unacceptable for clinical purposes.

A plot of the difference between the percentage change in Doppler cardiac output and that in thermal cardiac output versus the average of percentage changes measured by the two methods (fig 3) showed limits of agreement of −14·7 to +13·4%

A plot of the difference between the second thermal Doppler cardiac output and the second thermal cardiac output versus the average of these two measurements showed a bias of −0·02 l/min (95% CI −0·09 to +0·05 l/min). The limits of agreement were −0·55 to +0·51 l/min. Thus it is unlikely ($p < 0{\cdot}05$) that second thermal cardiac output and second thermal Doppler cardiac output in the same individual would differ by more than 0·55 l/min.

INTRA AND INTER OBSERVER VARIABILITY

Thermal cardiac output

The percentage differences were 4·3 (2·5)% for duplicate measurements by one observer and 5·1 (3·3)% for two independent observers.

Doppler cardiac output

The percentage differences were 4·1 (3·8)% for duplicate measurements by one observer and 5·7 (4·3)% for the two independent observers.

Discussion

Transoesophageal echocardiography has become established as a valuable method for postoperative monitoring of cardiac structure and left ventricular function in patients undergoing open-heart surgery. Transthoracic echocardiography often does not give good enough images in such patients. Transoesophageal echocardiography is facilitated in patients in the intensive care unit because they are sedated during ventilation. Furthermore, the technique gives an excellent view of the mitral apparatus and an optimal angle between the sound beam and transmitral flow. The thermodilution technique is the method most frequently used to measure cardiac output because it is simple to do with good precision.[10] Because prolonged maintenance of intraventricular catheters predisposes to the development of bacteraemia and endocarditis, the thermodilution catheter should be removed as soon as possible.

The objective of this study was to validate the use of the Doppler technique described as a reliable means of determining postoperative cardiac output. We found that the Doppler method on its own was not accurate enough for one off measurements of cardiac output. But once both thermal cardiac output and Doppler cardiac output had been measured simultaneously in a patient, subsequent transoesophageal Doppler measurement could be used to measure cardiac output without the need for a further thermodilution measurement.

There may be several reasons for the differences between Doppler cardiac output and thermal cardiac output. The angle of incidence between the sound beam and transmitral flow is an important determinant of the accuracy of Doppler measurements of blood velocity. Angles of incidence of $\leqslant 20°$ have little influence on velocity calculations because their cosine is nearly unity. The transthoracic apical window gives an angle of $\leqslant 20°$ between the sound beam and transmitral flow, whereas the transoesophageal approach limits the number of views that can be obtained and this results in an angle more than 20° between the sound beam and the transmitral flow. In our study we corrected for the angle of incidence in all measurements. However, there may still be an appreciable angle of incidence between the ultrasound beam and the real vectorial force of transmitral flow. The transoesophageal four chamber view is similar to the apical image

Table 1 Data from Doppler echocardiographic and thermodilution techniques

Patient No	Age (yr)	Sex	Operation	Doppler cardiac output	Thermal cardiac output				
					#1	#2	#3	Mean	SD
1	68	M	CABG	3·01	2·61	2·44	2·49	2·51	0·07
2	62	F	CABG	2·44	2·79	2·85	3·00	2·88	0·09
3	66	F	CABG	2·82	3·82	3·95	4·11	3·96	0·12
4	57	M	CABG	1·88	2·43	2·56	2·55	2·51	0·06
5	44	M	CABG	3·05	4·26	3·88	3·92	4·02	0·17
6	54	F	CABG	2·40	3·88	3·93	4·09	3·97	0·09
7	55	M	CABG	2·60	2·85	3·08	3·11	3·01	0·12
8	68	M	CABG	3·53	2·69	2·83	2·92	2·81	0·09
9	67	M	CABG	5·40	5·71	5·75	5·85	5·77	0·06
10	51	M	CABG	2·74	3·78	3·61	3·47	3·62	0·13
11	55	F	CABG	2·41	2·17	2·02	2·05	2·08	0·06
12	67	M	CABG	4·92	4·95	4·96	5·21	5·04	0·12
13	49	F	CABG	1·94	3·64	3·51	3·56	3·57	0·05
14	52	M	CABG	2·87	4·45	4·39	4·61	4·48	0·09
15	62	M	CABG	1·75	1·71	1·66	1·66	1·68	0·02
16	54	M	CABG	2·83	5·39	5·22	5·11	5·24	0·12
17	53	M	CABG	2·21	2·48	2·71	2·55	2·58	0·10
18	63	F	CABG	2·51	2·47	2·61	2·61	2·56	0·07
19	69	F	CABG	2·65	2·88	2·84	2·95	2·89	0·05
20	48	M	CABG	2·45	3·06	2·95	2·81	2·94	0·10
21	56	M	CABG	2·26	4·31	4·33	4·09	4·24	0·11
22	54	M	CABG	2·09	4·31	4·29	4·46	4·35	0·08
23	49	F	CABG	2·57	4·22	4·31	3·99	4·17	0 13
24	59	F	CABG	1·53	3·65	3·51	3·49	3·55	0·07
25	60	M	CABG	4·32	5·10	5·33	4·95	5·13	0·16
26	65	F	CABG	2·41	5·11	5·02	5·01	5·05	0·04
27	53	M	CABG	2·82	3·91	3·84	3 76	3·84	0·06
28	62	M	CABG	1·47	3·95	3·77	3·78	3·83	0·08
29	51	M	CABG	2·03	3·91	4·02	4·05	3·99	0·06
30	47	F	CABG	2·70	3·44	3·38	3·52	3·45	0·06
31	58	F	CABG	3 34	3·79	3·97	3·91	3·89	0·07
32	53	M	CABG	2·64	4·21	4·29	4·19	4·23	0·04
33	66	M	CABG	2·19	3·65	3·78	3·95	3·79	0·12
34	61	M	CABG	2·34	3·15	3·04	2·88	3·02	0·11
35	55	M	CABG	1·87	2·45	2·54	2·42	2·47	0·05
36	57	F	CABG	2·54	3·41	3·36	3·59	3·45	0·10
37	49	F	CABG	1·96	2·01	2·09	2·01	2·04	0·04
38	20	M	AVR	3·22	4·37	4·51	4·50	4·46	0·06
39	55	M	AVR	3·01	2·67	2·77	2·81	2·75	0·06
40	34	F	AVR	5·40	5·02	4·54	4·76	4·77	0·20
41	51	F	AVR	3·29	3·75	3·85	4·08	3·89	0·14
42	46	M	AVR	3·20	5·02	5·09	5·01	5·04	0·04
43	33	M	AVR	3·06	2·65	2·65	2·76	2·69	0·05
44	61	M	AVR	3·25	5·37	5·15	5·17	5·23	0·10
45	27	M	AVR	3·36	4·45	4·36	4·05	4·29	0·17
46	55	F	AVR	3·18	3·31	3·39	3·47	3·39	0·07
47	39	M	AVR	3·24	4·19	4·06	3·85	4·03	0·14
48	40	M	AVR	4·48	5·72	5·66	5·67	5·68	0·03
49	31	M	AVR	3·80	4·78	4·72	4·71	4·74	0·03
50	29	F	AVR	3·34	2·38	2·28	2·32	2·33	0·04
51	37	F	AVR	3·20	3·91	3·82	3·98	3·90	0·07
52	52	F	AVR	4·37	6·05	6·16	5·88	6·03	0·12
53	71	M	ARO	4·77	5·59	5·78	5·41	5·59	0·15
54	68	M	ARO	2·99	2·26	2·24	2·35	2·28	0·05
55	50	F	ARO	2·27	3·20	3·15	3·08	3·14	0·05
56	61	F	ARO	1·82	3·11	3·29	3·35	3·25	0·10
57	32	M	ARO	3·04	3·76	3·55	3·71	3·67	0·09
58	50	M	ARO	2·58	4·85	5·12	4·89	4·95	0·12
59	43	F	ARO	2·20	2·79	2·76	2·64	2·73	0·06
60	75	F	ARO	1·62	2·21	2·40	2·34	2·32	0·08
61	63	M	ARO	3·55	4·44	4·58	4·49	4·50	0·06
62	52	M	ARO	2·20	2·77	2·60	2·57	2·65	0·09
63	38	F	ARO	2·49	2·39	2·36	2·18	2·31	0·09
64	55	M	ARO	3·20	4·15	4·03	3·87	4·02	0·11
65	56	M	TVP	4·03	5·60	5·67	5·64	5·64	0·03

Doppler cardiac output is the cardiac output determined by the Doppler technique (l·min^{-1}); thermal cardiac output is cardiac output determined by the thermodilution technique (l·min^{-1}); CABG, coronary artery bypass grafting; AVR, aortic valve replacement; ARO, aortic reconstructive operation; ascending aorta and/or aortic arch reconstruction by composite valve graft or graft only; TVP, tricuspid valvuloplasty.

Table 2 Statistical analysis by method of Bland and Altman

	Cardiac output (l·min^{-1}) Doppler cardiac output v thermal cardiac output	*% change in cardiac output by Doppler v thermal*	*Cardiac output (l·min^{-1}) second thermal Doppler cardiac output v second thermal cardiac output*
Bias	−0·85	− 0·6	−0·02
Limits of agreement	−2·53 to +0·83	−14·7 to +13·4	−0 55 to +0·51
95% confidence interval for bias	−1·05 to −0·65	− 2·3 to + 1·1	−0·09 to +0·05
95% confidence interval for upper part of agreement	+0·47 to +1·19	+10·4 to +16·4	+0·40 to +0·62
95% confidence interval for lower part of agreement	−2·89 to −2·17	−17·7 to −11·7	−0·66 to −0·44

Doppler cardiac output is the cardiac output determined by the Doppler technique. Thermal cardiac output is the cardiac output determined by the thermodilution technique. The second thermal cardiac output is the second measurement of thermal cardiac output after intervention. The second thermal Doppler cardiac output is the estimated second measurement of thermal cardiac output that was derived from both the first and second Doppler measurements and the first thermodilution measurement.

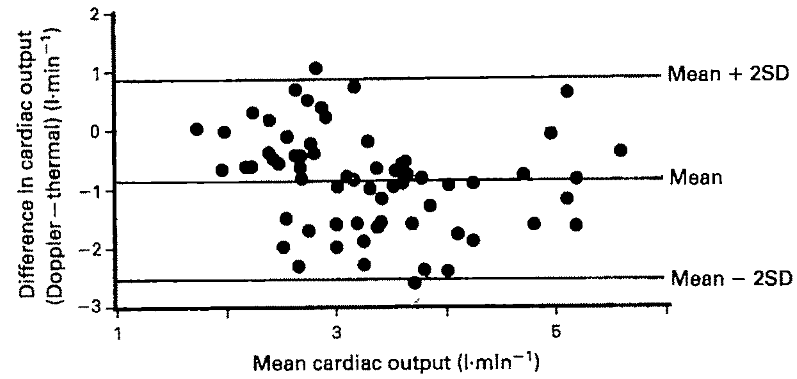

Figure 2 Difference between Doppler cardiac output and thermal cardiac output plotted against the mean of these two measurements. Doppler cardiac output is the cardiac output measured by the Doppler echocardiographic technique. Thermal cardiac output is the cardiac output measured by the thermodilution technique.

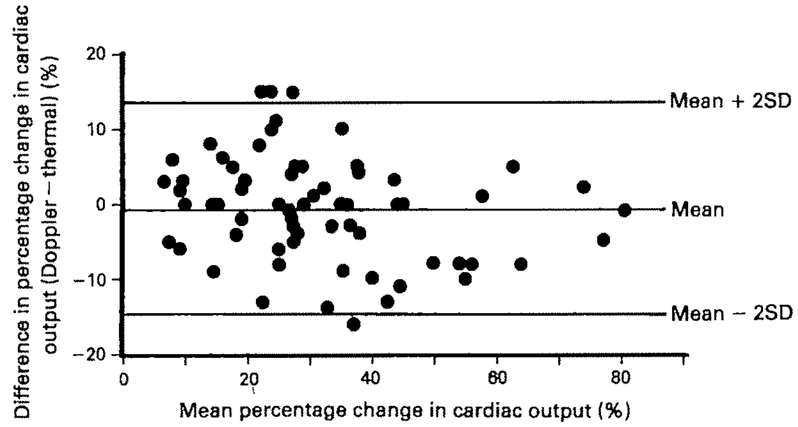

Figure 3 Difference between the percentage change in the Doppler cardiac output and that in the thermal cardiac output plotted against the mean of the percentage changes measured by the two methods.

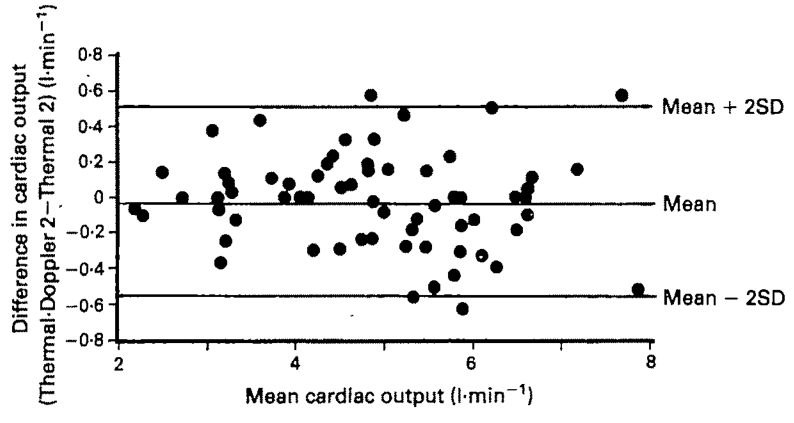

Figure 4 Difference between the second thermal Doppler cardiac output (thermal Doppler 2) and second thermal cardiac output (thermal 2) plotted against the mean of these two measurements. The second thermal cardiac output is the second measurement of cardiac output determined by thermodilution technique, the second thermal Doppler cardiac output is the estimated second measurement of thermal cardiac output, which was derived from both the first and second Doppler measurements and the first thermodilution measurement.

obtained with surface echocardiograms, but it does not include the true left ventricular apex.[11] Thus the cross sectional imaging plane may not be identical with the long axis of the left ventricle. However, because the precise angle of incidence in three dimensions usually can not be determined with certainty, we did not correct for an estimated angle between the imaging plane and the long axis of the left ventricle.

Another factor that may increase the difference between thermal cardiac output and Doppler cardiac output is the use of a single mitral annular diameter to estimate the cross sectional area of the annulus. Transthoracic echocardiography can be used to determine the cross sectional area of the annulus if it is assumed that the mitral annulus is elliptical with two orthogonal annular diameters[3 12] or circular with a single diameter.[3] Because transoesophageal cross sectional echocardiography mainly images horizontal sections it cannot measure two orthogonal annular diameters. Thus at present the only practical alternative is to calculate the area from a single diameter measurement. When Ormiston *et al* measured the mitral annulus in healthy controls by cross sectional echocardiography they found that the mitral annulus was nearly circular.[13] Lewis *et al* reported that the mitral annular area derived from two orthogonal diameters was nearly identical with that derived from one diameter alone.[3] Therefore we assumed that the mitral annulus is circular and used the single measurement method.

Axial resolution in phased array cross sectional echocardiographs is precise, whereas lateral resolution remains less certain. From the four chamber view, the transoesophageal ultrasound beam is roughly perpendicular to the mitral annulus and this may be an additional factor in the large difference between the two measurements.

In this study, we assumed that the cross sectional area of the mitral annulus was constant throughout diastole. The size of the mitral annulus was reported to change during the cardiac cycle. Ormiston *et al*[13] found that it increased gradually by 12% from early diastole to end diastole. This change represents a small change in diameter because the annular diameter is related to the square root of area. Thus we measured the diameter of the mitral annulus at peak rapid filling flow velocity in our study.

Tricuspid or mitral regurgitation can influence measurements of cardiac output by both the thermodilution and Doppler techniques. Thermal cardiac output basically provides an assessment of cardiac output from the right side of the heart. Patients who have considerable tricuspid regurgitation cannot have their forward left heart output accurately estimated by the thermodilution technique,[14] and in those with mitral regurgitation the Doppler cardiac output obtained from transmitral flow was an overestimate.[3] Therefore, ideally, these techniques for measuring cardiac output should be applied in patients without valve regurgitation. This is almost impossible because tricuspid reurgitation was detected in 15–64% and mitral regurgitation in 38–43% of healthy people aged from 20 to 49 years.[15] Also both tricuspid and mitral regurgitation as detected by pulsed Doppler echocardiography increase with age in apparently healthy people aged ≥60 years.[16] Second, the presence of the thermodilution catheter itself causes some tricuspid regurgitation which might interfere with the thermodilution technique. Fortunately, the severity of both tricuspid and mitral regurgitation was less than +1 in all our subjects: any error related to valve regurgitation would affect both measurements and in any case is believed to be minimal.

Comparison of precordial and transoesophageal studies would have been helpful but was not possible. The poor sensitivity and image quality of transthoracic echocardiography, especially in patients after open heart surgery, interfere with measurements of Doppler cardiac output. Because it is unacceptable to perform transoesophageal Doppler measurements postoperatively in patients who have not been fully sedated or who have satisfactory images from the transthoracic technique we did not compare these two Doppler measurements.

We found that transoesophageal Doppler measurements of cardiac output from transmitral flow alone may be unreliable. However, once both thermal cardiac output and Doppler cardiac output are determined simultaneously, subsequent cardiac output can be estimated from a single measurement of transoesophageal Doppler cardiac output. This new method extends the applicability of measuring cardiac output by transoesophageal echocardiography to patients in sinus rhythm after cardiac surgery.

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EPIDEMIOLOGY

Comparison of trends in ischaemic heart disease between North Karelia, Finland, and Kaunas, Lithuania, from 1971 to 1987

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Abstract

***Objective*—To compare the long-term trends in mortality and attack rate of ischaemic heart disease in North Karelia, Finland, and in Kaunas, Lithuania, from 1971 to 1987.**

***Design*—Data on routine mortality statistics were obtained from the Central Statistical Office of Finland and from the Central City Archives of Kaunas. In addition, data from the community based myocardial infarction registers were used. The registers used similar diagnostic criteria and had operated in both areas during the entire study period.**

***Setting*—The province of North Karelia in Finland and the city of Kaunas in Lithuania.**

***Subjects*—The target populations were the people of North Karelia and Kaunas aged 35–64 years.**

***Main outcome measures*—Mortality from ischaemic heart disease and the attack rate of acute myocardial infarction.**

***Results*—In North Karelia mortality from ischaemic heart disease and the attack rate of acute myocardial infarction declined steeply both in men and women. This decline was accompanied by a decrease in total mortality. In Kaunas, both mortality and the attack rate increased in men but remained unchanged in women. In 1985 to 1987, age standardised total mortality per 100 000 inhabitants was similar in the two populations in men (1081 (95% confidence interval (CI) 1013 to 1149), in North Karelia; 1082 (95% CI 1032 to 1132), in Kaunas). The proportional mortality from ischaemic heart disease was considerably higher in North Karelia (40%) than in Kaunas (28%). In women, age standardised total mortality was lower in North Karelia (350 (95% CI 312–388)) than in Kaunas (440 (95% CI 413 to 467)). The proportional mortality from ischaemic heart disease in women was also higher in North Karelia (28%) than in Kaunas (13%).**

***Conclusions*—Despite the remarkable decline in the occurrence of ischaemic heart disease, it still remains the most important cause of premature mortality in North Karelia. In Kaunas ischaemic heart disease mortality and attack rate increased in men. Experiences from successful cardiovascular disease prevention programmes in western countries, such as the North Karelia Project, should be exploited to prevent an increasing epidemic of ischaemic heart disease in eastern Europe.**

(*Br Heart J* 1992;**68**:516–23)

During the late 1950s and the early 1960s several western countries, including Finland, experienced a considerable increase in mortality and morbidity from ischaemic heart disease.[1,2] At the end of the 1960s the province of North Karelia in eastern Finland had the highest ischaemic heart disease mortality ever recorded in the world.[3] In the early 1970s mortality from ischaemic heart disease started to decline in North Karelia where this development was enhanced by the community-wide prevention programme launched in 1972.[4] Similar trends have been described in several western countries.[1,2] Despite this decline ischaemic heart disease remains the leading cause of death in developed countries, accounting for nearly half of all deaths.[5] Furthermore, recent reports have indicated that eastern European countries are now facing an increase in ischaemic heart disease mortality equivalent to that experienced in many western countries in the 1960s.[2,6] Our knowledge of these trends is, however, sparse and mainly based on routine mortality statistics, which are not validated by uniform diagnostic criteria between populations and over time.

Since the early 1970s North Karelia, Finland,[4,7] and Kaunas, Lithuania,[8,9] have had registers for myocardial infarction based on similar methods and data collection procedures. This gave us an opportunity to compare the trends in ischaemic heart disease mortality and attack rates in a western population with those in an eastern European popula-

*Table 1 Populations of North Karelia and Kaunas by age group and sex**

	Age groups						
Sex and year	*35–39*	*40–44*	*45–49*	*50–54*	*55–59*	*60–64*	*Total*
				North Karelia			
Men:							
1973	5120	5385	5420	4648	4204	4097	28874
1978	4963	5116	5311	5110	4155	3607	28262
1986	7958	5680	5015	4737	4918	4103	32411
Women:							
1973	4706	5097	5557	5269	5086	5081	30796
1978	4614	4684	5153	5434	5046	4779	29649
1986	6621	5057	4678	4616	5283	5158	31413
				Kaunas			
Men:							
1972	11791	12445	7868	5315	4674	5444	47537
1978	14507	11800	11949	9534	5954	4056	57800
1986	13400	12996	11595	10797	9776	5817	64381
Women:							
1972	12700	12493	11112	7252	7289	7966	58812
1978	15009	13343	12865	11879	8950	6709	68755
1986	15524	14978	14176	12695	11987	10178	79538

*The mid-year populations of North Karelia were obtained from the Central Statistical Office of Finland. For Kaunas population data were obtained from the Central Statistical Office of Lithuania.

tion. Data from the myocardial infarction registers also meant that routine mortality statistics in these two areas could be validated.

Patients and methods

North Karelia is the easternmost province of Finland with a population of about 175 000. The area is rural with income mainly from agriculture and forestry. Kaunas is the second largest city of Lithuania with a population of slightly over 400 000. It is an industrial city (mechanical and electronic engineering and food processing) in the central part of the republic. Table 1 shows the population in the two areas according to age and sex.

PROCEDURES FOR THE REGISTRATION OF MYOCARDIAL INFARCTION EVENTS

The myocardial infarction register was started in Kaunas in 1971 and in North Karelia in 1972. Both registers have operated since then. Suspected cases of myocardial infarction were identified through the death certificates and the hospitals treating patients with myocardial infarction in North Karelia and Kaunas. In both areas during the whole study period it was the standard practice to admit to hospital all patients with symptoms who were suspected of having an acute myocardial infarction. In North Karelia, about two thirds of the cases of myocardial infarction are treated in the specialised Central Hospital. The evaluation of all suspected events and the diagnostic classification was done at the Central Hospital by the myocardial infarction register team. The diagnostic categories were assigned by one physician (HM) during the entire study period. In Kaunas most patients with myocardial infarction were treated in the cardiological departments of the four main hospitals where they were admitted through coronary care units. All suspected myocardial infarction events were screened and validated by the central myocardial infarction register team. There was a change in the register team after the first period 1971–1972. During 1971–1972 the Kaunas Myocardial Infarction Register was computerised as a part of the World Health Organisation Heart Attack Register Study.[10]

In Kaunas data for the entire period from 1973 to 1982 were not fully computerised. For practical reasons we decided to estimate the trends in ischaemic heart disease mortality and attack rate of myocardial infarction during three periods: 1971–1972 (1973–1974 in North Karelia), 1978–1980, and 1985–1987.

Period 1971–1972, 1973–1974

The World Health Organisation Heart Attack Register criteria[10] were used for the registration of acute myocardial infarction events both in North Karelia and in Kaunas. Kaunas participated in the World Health Organisation International Collaborative Study for Myocardial Infarction Community Registers, but the North Karelia Myocardial Infarction Register started soon after the end of the World Health Organisation study. In both areas the approach to registration of events was prospective ("hot pursuit") in that the collection of information from patients usually started when the patient was admitted to hospital.

Period 1978–1980

In North Karelia the myocardial infarction register continued during the 1970s and was based on the same diagnostic criteria and procedures and the hot pursuit technique. During this period Kaunas started to use a "cold pursuit" technique, where events leading to hospital admission were identified mainly from the hospital discharge lists. The diagnostic criteria for and classification of the events remained the same as during the earlier period.

Period 1985–1987

The World Health Organisation MONICA Project started in the early 1980s.[5] North Karelia joined the MONICA Myocardial Infarction Register Study in 1982 and Kaunas joined in 1983. Since then both registers have used the diagnostic criteria and the classification of myocardial infarction events recommended by the World Health Organisation MONICA Project.[11] The MONICA criteria for the classification of the events differ slightly from those of the previous World Health Organisation Heart Attack Register criteria.[12 13] During this period in North Karelia the approach to registration was still hot pursuit whereas Kaunas continued cold pursuit registration.

VALIDATION OF CASES OF SUSPECTED MYOCARDIAL INFARCTION

When a patient died within 28 days of the onset of symptoms it was regarded as a fatal event. Only one event was recorded within a 28 day period.

In North Karelia the completeness of registration was ascertained by regularly reviewing diagnoses on the hospital discharge lists of the whole province in the Central Hospital. Those who died outside the hospital were found by regular reviews of death certificates in the area and the diagnosis was confirmed by cross checking data in the myocardial infarction register against the computerised National Death Certificate Register. The diagnostic data for missing cases were validated before such cases were added to the myocardial infarction register. The consistency of the diagnostic classification of the registered cases during 1972–1977 was evaluated in a subsample. The reclassification of the events showed a 94% agreement.[7] In Kaunas the completeness of the registration was ascertained by a regular review of death certificates in the area and of the hospital discharge lists for hospitals in the city. Since 1978 every twentieth case has been recoded by two independent coders to establish the reliability of event registration.

DIAGNOSTIC CATEGORIES

To reduce the influence of changes in diagnostic criteria over time and the possible influence of the change from a hot pursuit to a cold pursuit technique in Kaunas, only cases in the diagnostic category "definite myocardial infarction" and fatal cases with diagnostic categories "possible myocardial infarction" or "insufficient data" were included in the analyses.[10 11] Definitions of these categories during the different study periods are given below.

In 1971–1972, 1973–1974, and 1978–1980[10]

Definite myocardial infarction—Typical electrocardiogram or equivocal electrocardiogram wih raised enzymes and history of typical or atypical pain or a typical history of pain with raised enzymes; or positive findings at necropsy.

Possible myocardial infarction—Fatal cases whether sudden or not where there was no good clinical or necropsy evidence for another cause of death with a history of typical or atypical pain, or of chronic ischaemic heart disease or necropsy evidence of chronic ischaemic heart disease.

Insufficient data—Fatal cases with no necropsy, no history of pain, no previous history of chronic ischaemic heart disease, and no other diagnosis.

In 1985–1987[11]

The diagnostic categories differed only slightly from the previous study periods. The diagnostic criteria were more strictly standardised and symptoms were described in more detail than previously. Serial Minnesota coding was introduced for the classification of electrocardiographic changes.

Definite myocardial infarction—Definite electrocardiogram; or probable electrocardiogram with abnormal enzyme concentrations and with symptoms that are typical or atypical or inadequately described; or ischaemic or noncodable electrocardiogram or electrocardiogram not available with abnormal enzyme concentrations and typical symptoms; or fatal cases with positive findings at necropsy.

Possible myocardial infarction or coronary death—Fatal cases whether sudden or not where there is no good evidence for another cause of death clinically or at necropsy, with symptoms typical or atypical or inadequately described; or without typical or atypical or inadequately described symptoms but with evidence of chronic ischaemic heart disease at necropsy, or with a good history of chronic ischaemic heart disease.

Insufficient data—Fatal cases with no necropsy, no history of typical or atypical or inadequately described symptoms, no previous history of chronic ischaemic heart disease, and no other diagnosis.

Standard 12 lead electrocardiograms were recorded in hospital cases in both areas during the whole study period. In the beginning electrocardiograms were classified on the basis of the Minnesota code according to the recommendations of the World Health Organisation Register Study.[14] After they joined the MONICA project both areas used serial Minnesota coding.

In both areas before the World Health Organisation MONICA Project cardiac enzyme classification was based on aspartate aminotransferase and lactate dehydrogenase determinations during the first time period: a 1·5 fold rise was categorised as "definite enzymes" Thus the criteria for "definite enzymes" in North Karelia and Kaunas were stricter than in the World Health Organisation Register Study. According to the protocol of that study[10] a rise above normal reference range for the laboratory was categorised as "definite enzymes". Since the beginning of the MONICA project a twofold rise has been required in both areas. Plasma concentrations of creatine kinase and its MB isoenzyme have been used in North Karelia since 1982 in 95–100% of cases. In Kaunas measurements of creatine kinase and its MB isoenzyme have been available since 1979 in about 50% of cases. In the remainder aspartate aminotransferase and lactate dehydrogenase were used.

ROUTINE MORTALITY STATISTICS

The data on death rates in North Karelia from 1971 to 1987 were obtained from the Central

Statistical Office of Finland (official mortality statistics). The diagnoses made by local physicians on the individual death certificates are reviewed in this office by a nosologist according to the guidelines of the *International Classification of Diseases* (ICD). The ICD 8th revision (ICD-8) was used in Finland until 1986 and ICD-9 since the beginning of 1987. In Kaunas no official mortality statistics were available but all the death certificates from 1971 to 1974 and from 1978 to 1987 were obtained from Central City Archives and computerised records were kept by the Kaunas Research Institute of Cardiology. The death certificates are filled in and coded by the physician certifying the death. Diagnoses on the death certificate are not checked up or recoded. ICD-8 was used until 1977 and ICD-9 since the beginning of 1978 in most hospitals and outpatient departments in Kaunas. Death certificates coded according to ICD-8 in 1978–1980 were recoded according to ICD-9 by the staff of the register group.

NECROPSY RATE

In North Karelia necropsy was performed on 27% of those who died of ischaemic heart disease in 1973–74 and 55% in 1985–1987. Whereas in Kaunas the frequency of necropsy decreased from 72% in 1971–1972 to 60% in 1985–1987.

STATISTICAL METHODS

The "attack rate" of acute myocardial infarction in our present study refers to all symptomatic events of acute myocardial infarction, whether first or recurrent. It thus includes fatal cases in the diagnostic categories of "definite myocardial infarction", "possible myocardial infarction", or "insufficient data", and nonfatal cases with "definite myocardial infarction". Age standardisation was performed by the direct method in five-year age groups and according to the World Standard Population.[15] Confidence intervals for the rates were calculated assuming the Poisson variation of the number of events within the age groups. Trends in attack rate and mortality were calculated by linear regression on logarithms of the annual rates. The trend (percentage of a continuous change per year) was reported as the regression coefficient multiplied by 100.

p Values $<0{\cdot}05$ were regarded as statistically significant. All the reported p values are two-tailed. The equality of the trends in slopes between Kaunas and North Karelia was not tested because of the apparent ambiguity in the interpretation of equality of trends when the actual mortality rates are very different. However, when one trend is significantly negative and the other one significantly positive there is no such ambiguity.

Results

Routine mortality statistics showed that mortality from ischaemic heart disease in North Karelian men aged 35–64 years decreased significantly from 1971 to 1987 (fig 1) by 2·3% per year (95% CI −2·9 to −1·6, p = 0·0001 according to regression analysis)). In Kaunas mortality increased by 2·4% per year (95% CI +1·3 to +3·6, p = 0·0005). In North Karelia mortality from ischaemic heart disease in women also declined significantly (fig 1) by 2·2%/year (95% CI −4·0 to −0·4, p = 0·02). In Kaunas mortality statistics based on death certificates showed a small (NS) increase in mortality from ischaemic heart disease (0·6% per year (95% CI −1·5 to +2·7, p = 0·54) by regression analysis.

Proportional mortality from ischaemic heart disease was higher in North Karelia than in Kaunas (table 2). During the early 1970s mortality from all causes in men was significantly higher in North Karelia than in Kaunas. This difference later disappeared. During the period 1985–1987 total mortality among men was similar for the two areas, but the proportion of all deaths caused by ischaemic heart disease was 40% in North Karelia but only 28% in Kaunas. In women total mortality was lower in North Karelia than in Kaunas, but the proportion of total mortality caused by ischaemic heart disease was clearly higher in North

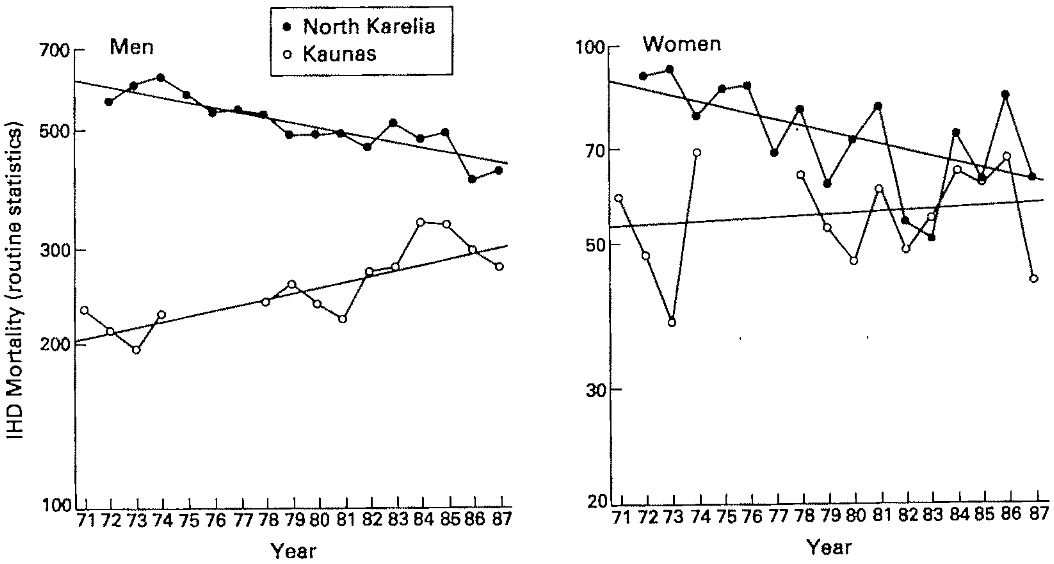

Figure 1 Trends in age standardised mortality (per 100 000 population) from ischaemic heart disease (expressed in logarithmic scale) during 1971 to 1987 according to the routine mortality statistics in men and women aged 35–64 years in North Karelia and Kaunas. Annual percentage changes based on linear regression (95% confidence interval) are −2·3 (−2·9 to −1·6, p = 0·0001) and +2·4 (+1·3 to +3·6, p = 0·0005) in men and −2·2 (−4·0 to −0·4, p = 0·02) and +0·6 (−1·5 to +2·7, p = 0·54) in women in North Karelia and Kaunas respectively.

Table 2 Age standardised ischaemic heart disease, cardiovascular disease, and total mortality (95% confidence interval) and the proportion of ischaemic heart disease mortality from total mortality (%) in men and women aged 35–64 years in North Karelia and Kaunas. Rates are based on the routine mortality statistics and are expressed as a mean of each two or three year period

	Annual mortality rate per 100 000 population			
Age, sex, and period	*Ischaemic heart disease (95% CI)*	*Cardiovascular disease (95% CI)*	*All causes (95% CI)*	*Proportional mortality from ischaemic heart disease (%)*
		North Karelia		
Men:				
1973–1974	610 (546 to 674)	800 (727 to 873)	1380 (1280 to 1480)	44
1978–1980	503 (455 to 551)	663 (608 to 718)	1256 (1172 to 1340)	40
1985–1987	437 (394 to 480)	573 (524 to 622)	1081 (1013 to 1149)	40
Women:				
1973–1974	85 (64 to 106)	182 (150 to 214)	415 (365 to 465)	20
1978–1980	71 (55 to 87)	148 (124 to 172)	376 (336 to 416)	19
1985–1987	70 (54 to 86)	125 (103 to 147)	350 (312 to 388)	20
		Kaunas		
Men:				
1971–1972	222 (189 to 255)	347 (305 to 389)	1075 (1003 to 1147)	21
1978–1980	245 (218 to 272)	367 (334 to 400)	1221 (1162 to 1280)	20
1985–1987	303 (276 to 330)	436 (404 to 468)	1082 (1032 to 1132)	28
Women:				
1971–1972	53 (40 to 66)	133 (111 to 155)	472 (431 to 513)	11
1978–1980	55 (44 to 66)	126 (109 to 143)	475 (444 to 506)	11
1985–1987	58 (48 to 68)	134 (119 to 149)	440 (413 to 467)	13

Karelia (table 2). Among men the proportion of mortality from all cardiovascular diseases caused by ischaemic heart disease was constant in North Karelia (76%) and increased in Kaunas from 64% to 69%. Among women the proportion was around 50% in North Karelia and around 42% in Kaunas.

The attack rate of myocardial infarction decreased steeply (2·6% per year, 95% CI −3·6 to −1·5, p = 0·0009) among North Karelian men aged 35–64 years during the study period (fig 2, table 3). In Kaunas the attack rate increased by 1·0% a year (95% CI +0·2 to +1·9, p = 0·02). The regression based decline in the attack rate of myocardial infarction from 1973 to 1987 was 44% in North Karelia and the increase in Kaunas was 17%. The decrease in the attack rate in North Karelia was caused by a change in the younger age groups (35–54 years) whereas in Kaunas the increase mainly occurred among younger men (table 3). In women the slight decreases in the attack rate of myocardial infarction in both areas were not statistically significant (table 3). The regression based decrease in North Karelian women was 0·6% per year (95% CI −2·0 to +0·9, p = 0·38) and in Kaunas 1·1% per year (95% CI −4·0 to +1·85, p = 0·40). Mortality from myocardial infarction validated against the myocardial infarction register showed a downward trend in North Karelia whereas in Kaunas there was no significant trend (fig 3, table 4). The regression based decrease in North Karelian men was 2·6% per year (95% CI −3·5 to −1·7, p = 0·0004) and in men in Kaunas there was an increase of 0·9% per year (95% CI −0·1 to +1·9, p = 0·07). Among women both in North Karelia and Kaunas the data from the myocardial infarction register suggested a decline (NS). The regression based decrease in North Karelian women was 1·7% per year (95% CI −3·4 to +0·1, p = 0·06) and in Kaunas 2·6% per year (95% CI −6·3 to +1·2, p = 0·15).

Although in men the differences in the attack rate and mortality of myocardial infarction between the two areas decreased over time, the attack rate of myocardial infarction during 1985–1987 remained approximately twice as high in North Karelia as in Kaunas (table 3). In 1985–1987 mortality from myocardial infarction according to the myocardial infarction register data was 68% higher in men and 58% higher in women in North Karelia than in Kaunas (table 4).

Discussion

Our study assessed long-term trends in the occurrence of ischaemic heart disease from routine mortality statistics and myocardial infarction registration in two countries with different genetic backgrounds and different living conditions. Few registries can provide such long-term data, and of these Kaunas is the only one in eastern Europe, in an area where mortality from ischaemic heart disease is still increasing. During the study period, however, several changes may have affected the comparability of the results over time and between the two centres. For routine mortality statistics, one is the change from ICD-8 to ICD-9. In North Karelia this occurred at the beginning of 1987. Hence only the last year could be affected. Even in that year, however, ischaemic heart disease mortality both in men and women was well in line with the previous years and the change in the ICD revision did not substantially affect the mortality trend. Furthermore,

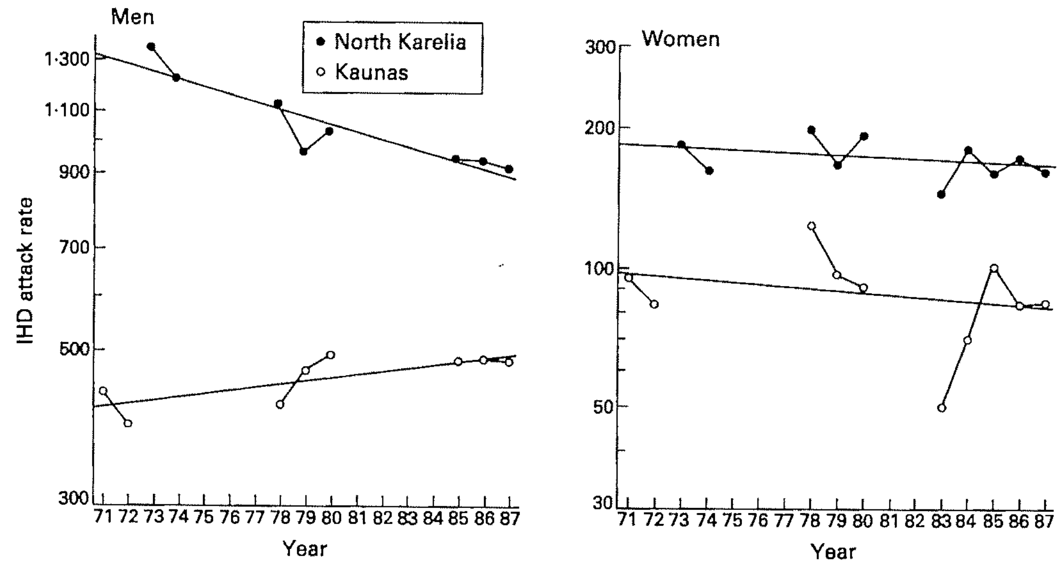

Figure 2 Trends in age standardised attack rates (per 100 000 population) of ischaemic heart disease (expressed in logarithmic scale) during 1971 to 1987 according to data from the myocardial infarction register in men and women aged 35–64 years in North Karelia and Kaunas. Annual percentage changes based on linear regression (95% confidence interval) are $-2{\cdot}6$ ($-3{\cdot}6$ *to* $-1{\cdot}5$, $p = 0{\cdot}0009$) *and* $+1{\cdot}0$ ($+0{\cdot}2$ *to* $+1{\cdot}9$, $p = 0{\cdot}02$) *in men and* $-0{\cdot}6$ ($-2{\cdot}0$ *to* $+0{\cdot}9$, $p = 0{\cdot}38$) *and* $-1{\cdot}1$ ($-4{\cdot}0$ *to* $+1{\cdot}85$, $p = 0{\cdot}40$) *in women in North Karelia and Kaunas respectively.*

in most industrialised countries the change from ICD-8 to ICD-9 caused only a small degree of discontinuity.[16] Thus the change of ICD revision in 1978 in Kaunas seems unlikely to have had much effect. The methods used by the myocardial infarction registers were standardised according to common criteria in both areas. In addition to the fatal cases, only definite myocardial infarctions in living patients were included in the present analyses to enhance the comparability of findings. It has been suggested that use of these categories is the best basis for comparisons between the centres using different methods, such as the hot pursuit and cold pursuit techniques of registration.[17] On the other hand, workers in Auckland, New Zealand, reported that only 82% of cases, classified as "definite myocardial infarctions" according to the old World Health Organisation criteria, remained as "definite myocardial infarctions" when the MONICA criteria were applied.[18] This could lead to spurious decline in the attack rates both in North Karelia and Kaunas in the early 1980s. However, the old register criteria of the World Health Organisation relied on some subjective assessment, especially of electrocardiographic findings.[10] Therefore it is not clear whether the results of the Auckland group are repeatable elsewhere. Also the fact that criteria for "definite abnormal cardiac enzymes" were stricter both in North Karelia and Kaunas than in the World Health Organisation register in general, tends to reduce the possible differences between the two criteria. The introduction of more sensitive cardiac enzymes, creatine kinase and its MB

Table 3 Number of cases and age standardised attack rates of acute MI (95% confidence interval) in men and women aged 35–64 years in North Karelia and Kaunas by age. Rates are based on the data of the myocardial infarction registers and expressed as a mean of each two or three year period

	Number of cases						*Attack rate/year/100 000 population*	
	Age group						*Total*	*Total*
Area, sex, and period	*35–39*	*40–44*	*45–49*	*50–54*	*55–59*	*60–64*	*35–54 (95% CI)*	*35–64 (95% CI)*
				North Karelia				
Men:								
1973–1974	35	72	102	152	169	242	862 (771 to 953)	1287 (1194 to 1380)
1978–1980	29	58	119	230	239	244	669 (405 to 733)	1035 (966 to 1104)
1985–1987	35	52	91	163	252	293	529 (469 to 583)	920 (858 to 982)
Women:								
1973–1974	1	5	12	14	28	66	73 (47 to 99)	174 (143 to 205)
1978–1980	2	6	11	29	68	84	73 (52 to 94)	187 (160 to 214)
1985–1987	1	3	11	21	54	93	60 (40 to 80)	166 (141 to 191)
				Kaunas				
Men:								
1971–1972	15	38	43	56	55	134	242 (201 to 283)	414 (368 to 460)
1978–1980	24	78	125	181	140	133	300 (270 to 330)	465 (428 to 502)
1985–1987	40	68	125	204	218	220	302 (273 to 331)	483 (450 to 516)
Women:								
1971–1972	0	4	6	8	36	49	23 (12 to 34)	89 (71 to 107)
1978–1980	2	5	11	33	50	90	32 (23 to 41)	106 (91 to 121)
1985–1987	2	2	13	26	56	104	25 (17 to 33)	83 (71 to 95)

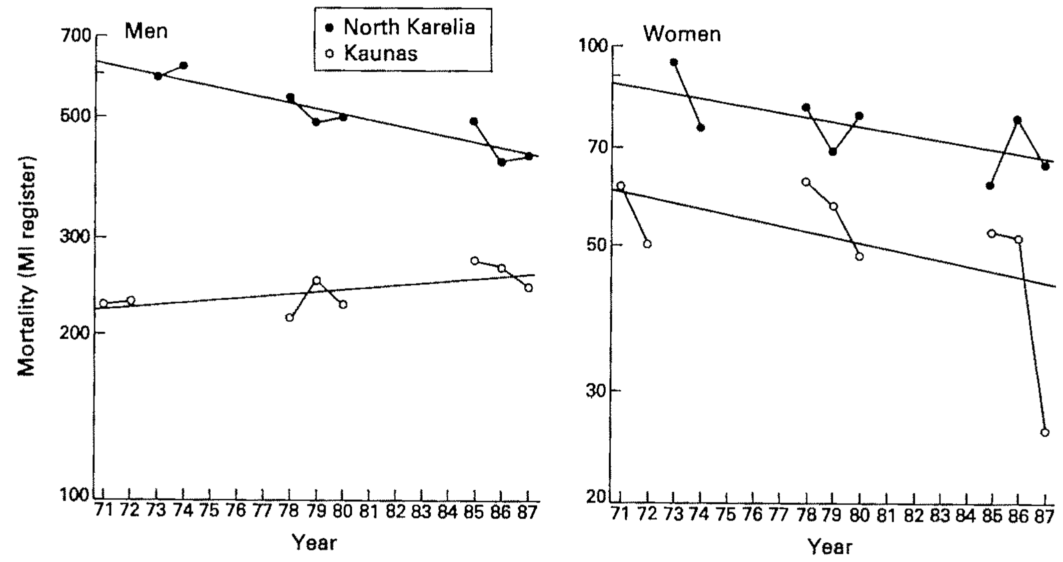

Figure 3 Trends in age standardised mortality (per 100 000 population) from ischaemic heart disease (expressed in logarithmic scale) during 1971 to 1987 according to data from the myocardial infarction register in men and women aged 35–64 years in North Karelia and Kaunas. Annual percentage changes based on linear regression (95% confidence interval) are −2·6 (−3·5 to −1·7, p = 0·0004) and +0·9 (−0·1 to +1·9, p = 0·07) in men and −1·7 (−3·4 to +0·1, p = 0·06) and −2·6 (−6·3 to +1·2, p = 0·15) in women in North Karelia and Kaunas, respectively.

isoenzyme, has probably also had some effect on the trends. The Minnesota Heart Survey investigators showed that the addition of these enzymes to the diagnostic criteria increases the rate of definite myocardial infarctions.[19] This has probably lessened the decline of the attack rates in North Karelia and may have contributed to the increase in men in Kaunas, although creatine kinase and its MB isoenzyme were measured in only about 50% of the cases in Kaunas. On the other hand, the cutpoint for "definite abnormal enzymes" was raised from an increase of 1·5-fold to 2-fold at the start of the MONICA project, which would counter these effects.

In fatal cases the high necropsy rate in Kaunas increases the diagnostic accuracy and reduces the influence of other changes in methods. At the end of the observation period the necropsy rates were similarly high in both areas but at the beginning of the 1970s the necropsy rate in North Karelia was considerably lower than that in Kaunas. The necropsies in North Karelia were, however, focused on the cases where there was insufficient clinical information.[20] Thus the different necropsy rates at the start of the study are unlikely to have caused a substantial difference in the diagnostic classification between the areas.

Despite several potential pitfalls, which are inevitable in this kind of long-term comparison, we believe that our study gives a representative picture of the trends in the mortality and attack rate of myocardial infarction in both areas. The study confirmed that for myocardial infarction in North Karelia there was a con-

Table 4 Number of cases and age standardised mortality from ischaemic heart disease (95% confidence interval) in men and women aged 35–64 years in North Karelia and Kaunas by age. Rates are based on the data of the myocardial infarction registers and expressed as a mean of each two or three year period

	Number of cases						*Mortality rate/year/100 000 population*	
	Age group						*Total*	*Total*
Area, sex, and period	*35–39*	*40–44*	*45–49*	*50–54*	*55–59*	*60–64*	*35–54 (95% CI)*	*35–64 (95% CI)*
				North Karelia				
Men:								
1973–1974	8	30	42	67	81	138	350 (292 to 408)	604 (541 to 667)
1978–1980	11	23	45	112	122	140	290 (248 to 332)	509 (461 to 557)
1985–1987	13	26	35	75	120	154	230 (192 to 268)	438 (395 to 481)
Women:								
1973–1974	0	2	3	6	17	35	25 (10 to 40)	84 (63 to 105)
1978–1980	0	2	3	12	27	38	25 (13 to 38)	76 (59 to 93)
1985–1987	1	2	4	11	17	39	29 (15 to 43)	68 (52 to 84)
				Kaunas				
Men:								
1971–1972	4	14	19	26	33	89	104 (77 to 131)	228 (194 to 262)
1978–1980	9	32	56	79	72	79	130 (110 to 150)	232 (205 to 259)
1985–1987	17	22	65	102	123	136	143 (123 to 163)	261 (236 to 286)
Women:								
1971–1972	0	3	3	1	27	31	8 (12 to 14)	55 (41 to 69)
1978–1980	0	2	4	14	25	55	13 (7 to 19)	57 (46 to 68)
1985–1987	2	1	7	8	28	59	11 (6 to 16)	43 (35 to 51)

siderable decline in mortality and attack rate from the beginning of the 1970s till 1987. Similar declines in ischaemic heart disease mortality have been reported in many western countries,[1,2,21] but the trends in attack rates or hospital admissions are not so well established.[22] The decline in ischaemic heart disease mortality in North Karelia was accompanied by similar decline in cardiovascular disease mortality and in total mortality. Thus no other cause of death has replaced ischaemic heart disease in men and women of this age group. On the other hand, the results suggest that in men in Kaunas ischaemic heart disease mortality is increasing, as it is in many other eastern European countries.[1,2,23] Nor was there a decline in total mortality in men in Kaunas. The levels of conventional risk factors for ischaemic heart disease in many eastern European populations have been increasing and at the present they are higher than in most other European populations.[6,24,25]

In North Karelia mortality estimates based on routine mortality statistics and on the myocardial infarction register were similar. In Kaunas routine mortality statistics based on death certificates showed a 41% increase in ischaemic heart disease mortality in men aged 35–64 years during 1971 to 1987, whereas the myocardial infarction register data showed an increase of only 17%. In women there was a similar discrepancy: an increase of 10% based on routine mortality statistics but a decrease of 44% based on the myocardial infarction register. This suggests that routine statistics may have exaggerated the increase in mortality from ischaemic heart disease in Kaunas. This suggestion accords with the increase in proportional mortality from ischaemic heart disease in Kaunas.

Despite the remarkable decline in mortality from ischaemic heart disease in North Karelia it still remains considerably higher than that in Kaunas. This emphasises the need to continue preventive and treatment efforts for ischaemic heart disease in Finland. In Kaunas the continuing increase, particularly among young men, is alarming and resembles the situation in many western countries in the early 1960s. The experiences of successful prevention programmes, such as the North Karelia project, should be exploited to prevent the increasing epidemic of ischaemic heart disease in eastern European countries.

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Br Heart J 1992;68:524–6

CASE REPORTS

Intravascular ultrasound to assess left main stem coronary artery lesion

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Abstract

A man of 70 underwent coronary arteriography for the assessment of angina. The appearance of the left coronary main stem was slightly abnormal but no definite stenosis could be delineated. Intracoronary ultrasound examination with a 4·8 French intravascular ultrasound probe showed an extensive plaque in the distal left main stem and proximal left anterior descending coronary artery, with a shelf-like projection causing 60% narrowing at one point in the distal left main stem. Since coronary bypass surgery the patient has been free of angina.

(*Br Heart J* 1992;68:524–6)

Intravascular ultrasound examination is a new method of vascular imaging that shows the lumen and cross sectional anatomy of the vessel wall. Intravascular ultrasound probes are now small enough to enter the coronary arterial tree. Several reports have shown the research potential of intracoronary ultrasound but its clinical usefulness has yet to be defined. We report the use of intracoronary ultrasound to demonstrate left main stem disease not visualised satisfactorily on diagnostic fluoroscopy.

Case report

A fit 70 year old medical practitioner presented to casualty with persistent severe chest pain at rest. Over the preceding three months he had experienced short episodes of chest pain that was not consistently related to physical exertion and occasionally had occurred at rest, lasting 5–10 minutes. The chest pain became less severe but no less frequent after he started to take diltiazem and long-acting nitrate regularly. He had smoked 20 cigarettes per day until two months before; there was no family history of myocardial infarction or angina.

Physical examination was unremarkable, with no stigmata of hyperlipidaemia and no signs of cardiac failure. The electrocardiogram recorded in the casualty department during chest pain showed atrial tachycardia with non-specific ST-T changes (fig 1A); a normal electrocardiogram was recorded later when the patient was pain free (fig 1B). The chest *x* ray was normal.

Coronary arteriography showed only a suggestion of abnormality of the distal left main stem coronary artery in one view (right anterior oblique 30°), other views were normal in appearance. The left anterior descending, circumflex, and dominant right coronary arteries were normal. Left ventriculography in the right anterior oblique projection showed normal contraction.

Because of the suspicious appearance of the left main stem, further investigation was performed to assess the possible need for coronary artery surgery. Cardiac catheterisation was performed via the femoral approach and the left coronary ostium was intubated with a 9 French short-tipped left Judkins guiding catheter (Medtronic, UK). Heparin 5000 units and diazepam 5 mg were given intravenously. High resolution digital angiograms (Siemens Digitron III) acquired during contrast injection showed a fine line of reduced contrast density extending obliquely across the diameter of the distal left main stem, best visualised in the right anterior oblique projection with caudo-cranial angulation (fig 2).

A 0·014 inch high torque floppy guide wire was passed into the left anterior descending artery. A 4·8 French monorail intravascular ultrasound probe (Sonicath 90-2273, Boston Scientific, Watertown, Massachussetts) was connected to a Diasonics ultrasound machine (Diasonics, Milpitas, California) modified for the acquisition and display of intravascular ultrasound images. The ultrasound probe was advanced over the guide wire and cross sectional images were obtained of the entire left main stem and proximal left anterior descending artery (fig 3). These showed an eccentric plaque extending from the distal left main stem into the proximal left anterior descending artery. In the distal left main stem the plaque was shelf-like and at the point of maximum encroachment reduced the lumen by approximately 60% over an axial distance of 1 mm. The axial extent of the whole plaque was approximately 10 mm.

The patient tolerated the procedure well and returned to the ward without any chest discomfort or electrocardiographic changes. Because of the history of episodes of anginal

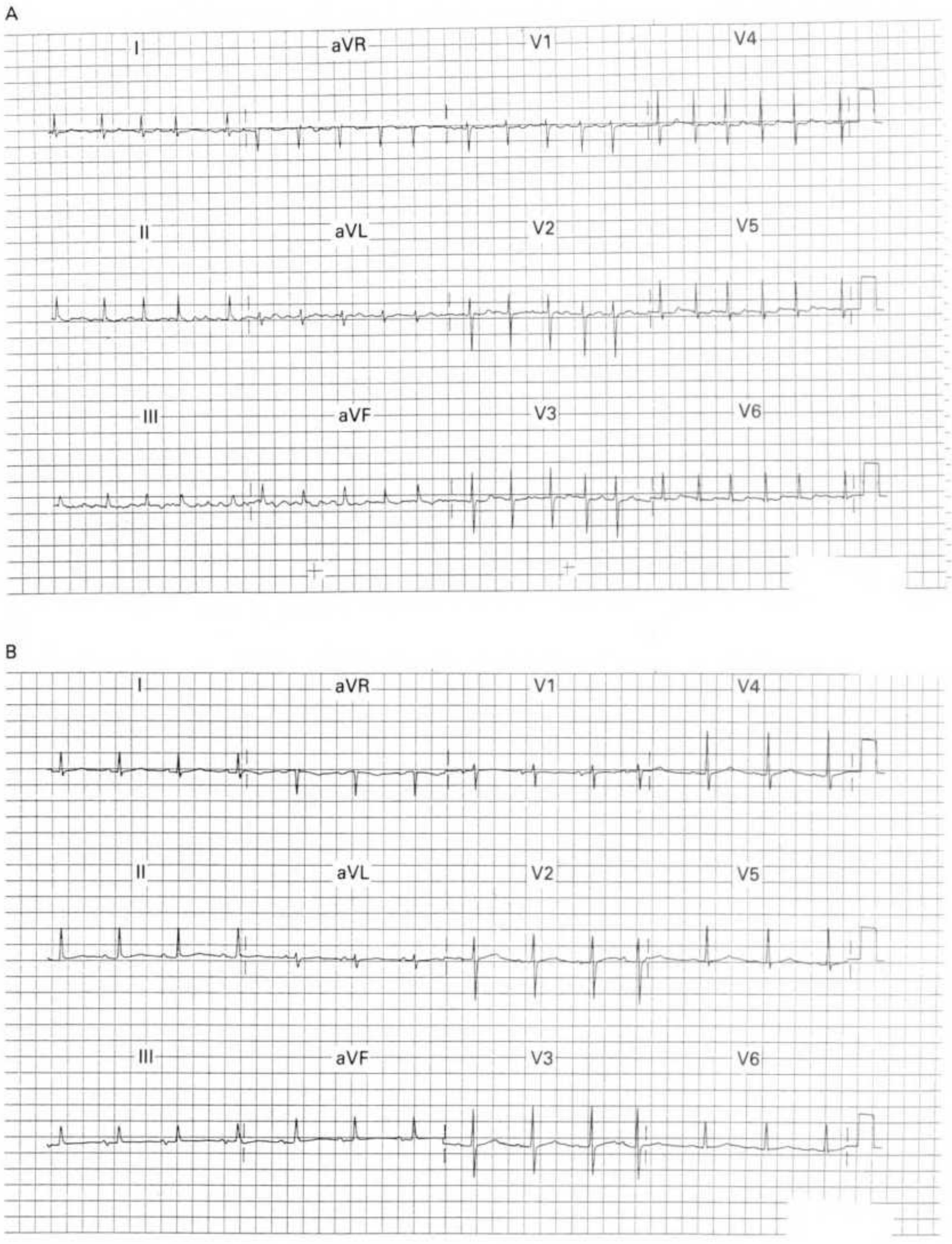

Figure 1 (A) Electrocardiogram during an episode of chest pain. (B) Electrocardiogram without chest pain.

pain at rest together with the ultrasound appearances of clinically significant left main stem disease, elective coronary artery surgery was performed. Vein grafts were inserted into the mid-portion of the left anterior descending artery and into a large anterolateral circumflex branch. The patient made an uncomplicated recovery and was discharged eight days postoperatively. There have been no further episodes of angina.

Discussion

The requirement for precise and immediate knowledge during performance of interventional vascular techniques has led to the development of intravascular ultrasound. Resolution of intimal dissections, the detail of the vessel wall, and the nature of the material

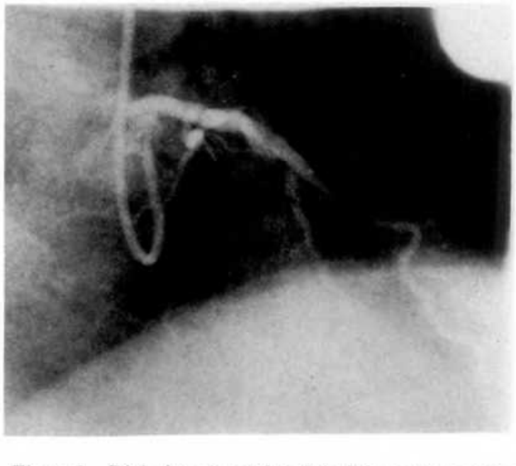

Figure 2 Digital angiography of the left coronary artery in the right anterior oblique projection with caudo-cranial angulation.

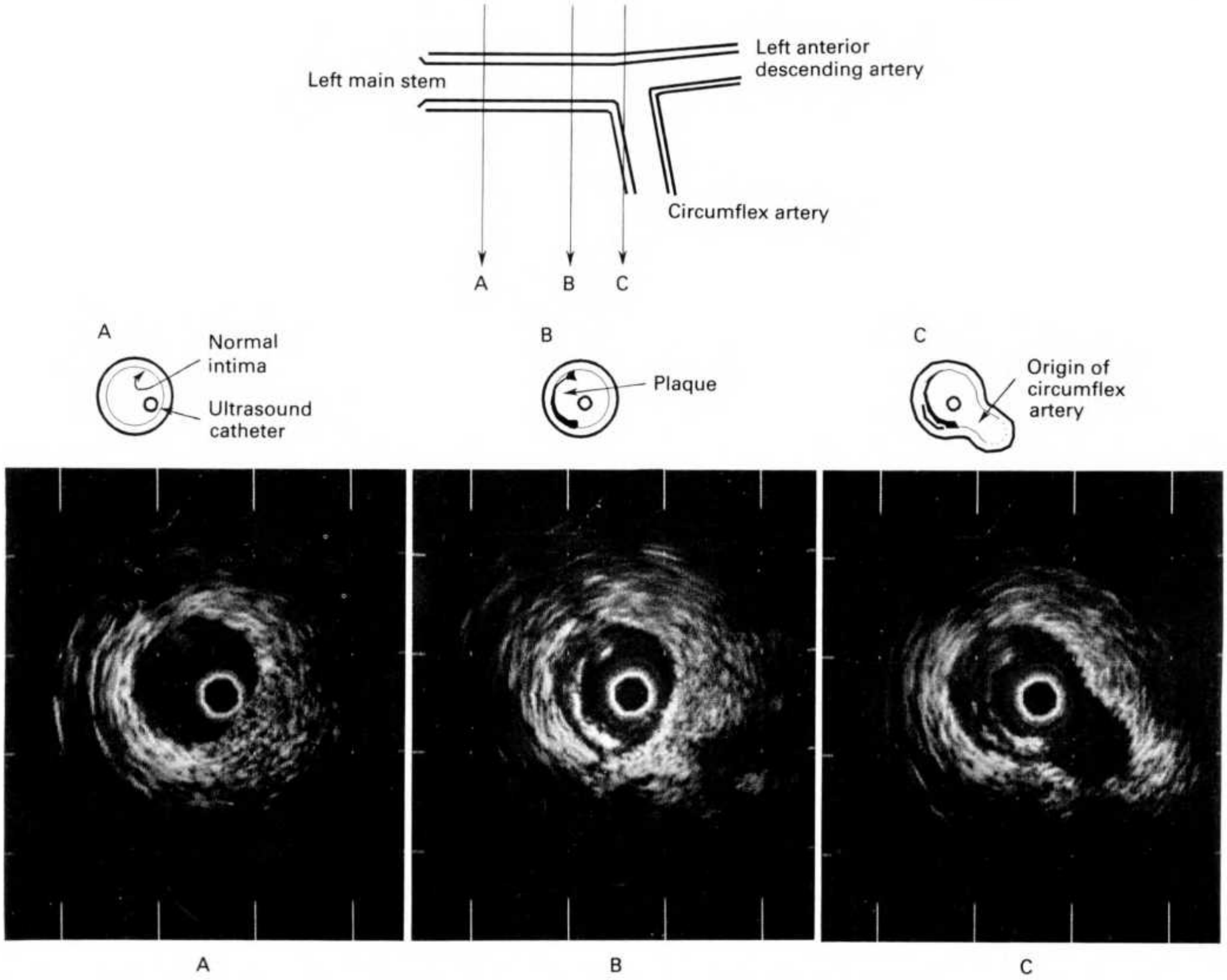

Figure 3 Intracoronary ultrasound appearances of the left coronary artery: (A) proximal left main stem; (B) distal left main stem, with eccentric plaque; (C) distal left main stem showing the origin of the circumflex artery and an eccentric plaque.

causing the stenosis or obstruction still elude the operator who relies on the *x* ray image.

Contrast arteriography is the currently accepted method for defining the presence and severity of disease in peripheral and coronary arteries. This technique has limitations: it underestimates the extent and severity of disease,[1] it has significant intra and inter observer error, it may be difficult to assess tortuous segments of vessel, overlying vessels may obscure disease, and it may be difficult to obtain high quality images during interventional procedures.[2]

The case for ultrasound, rather than direct visualisation with a fibreoptic angioscope in this case, is made by the fact that ultrasound can pass through blood and the technique does not require blood replacement during visualisation. This may not be very important for peripheral vessels but is critical in the coronary and cerebral circulations, particularly if frequent images are required. This patient had no demonstrable collateral supply from the right coronary artery and we did not know whether he would have tolerated an extensive period without oxygenated fluid in the left coronary system.

Sound waves can penetrate tissue and show vessel wall structure in depth. Morphological detail can be seen and it is possible to discriminate between elastin amd muscular arteries and to see lipid (hypo-echoic), fibromuscular tissue (soft echoes), collagen rich fibrous tissue (bright echoes), and calcified tissue (bright echoes with shadowing behind).[3 4] It is easy to discern tissue differences within the pathological area in this patient's images. No pathological correlation is available in this case but a hypo-echoic area was discerned behind the echo-dense luminal surface (fig 3C), that was compatible with a lipid lake behind collagen-rich fibrous tissue. This appearance suggests a newer plaque.

Ultrasound has other advantages—it is safe and the images are readily understood by the operator. It can be incorporated with treatment technologies and may therefore become the on-board diagnostic element of combination devices such as directional atherectomy and laser. It can be combined with Doppler images and pictorial three dimensional flowfield representation is already possible.[5]

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Br Heart J 1992;**68**:527–8

Rapid reversal of heart failure in a patient with phaeochromocytoma and catecholamine-induced cardiomyopathy who was treated with captopril

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Abstract

A patient with a phaeochromocytoma and severe left ventricular heart failure caused by a catecholamine-induced cardiomyopathy is described. The clinical signs of congestive heart failure resolved rapidly on treatment with captopril and myocardial performance became normal within two weeks of medical treatment with captopril for one week and with captopril in combination with phenoxybenzamine for another week.

(*Br Heart J* 1992;**68**:527–8)

Despite active secretion of catecholamines phaeochromocytoma is associated with normotension or even with considerable hypotension in up to 30% of cases.[1] We report the case of a patient with a phaeochromocytoma and acute and severe left ventricular heart failure caused by a histologically confirmed catecholamine-induced cardiomyopathy.

Case report

A 42 year old man was admitted to a district hospital complaining of a chronic unproductive cough. Five years earlier his heart size had been normal, but two months before admission a slight cardiac enlargement had been noticed on a chest *x* ray. During a flexible bronchoscopy (to rule out a bronchial adenoma) he became tachycardiac and hypertensive (220/120 mm Hg). Propranolol (1 mg) was injected intravenously. Respiratory distress rapidly developed and he needed artifical ventilation. A chest *x* ray showed pulmonary oedema and an enlarged heart, and the electrocardiogram showed sinus tachycardia and ST segment elevations in leads V1 to V6. M mode and cross sectional transthoracic echocardiography showed global hypokinesia of the left ventricle. Treatment with glyceryl trinitrate, dopamine, dobutamine, and diuretics was started. The patient was transferred to the intensive care unit in our hospital.

A coronary angiogram did not show left main stem disease. Left ventriculography showed global hypokinesia despite inotropic stimulation. The left end diastolic pressure was increased to 17 mm Hg and the ejection fraction was reduced to 46%. An endomyocardial biopsy specimen showed focal fibre necrosis and infiltration of monocytes and lymphocytes (figure).

During the next two days the patient's blood pressure fluctuated considerably. On the third day extubation could be performed and treatment with vasopressors was stopped. The patient became again hypertensive; systolic blood pressure peaked at over 230 mm Hg. Medical treatment with diuretics and nifedipine was unsuccessful. Captopril, however, controlled blood pressure and improved the clinical signs of left ventricular failure within eight hours.

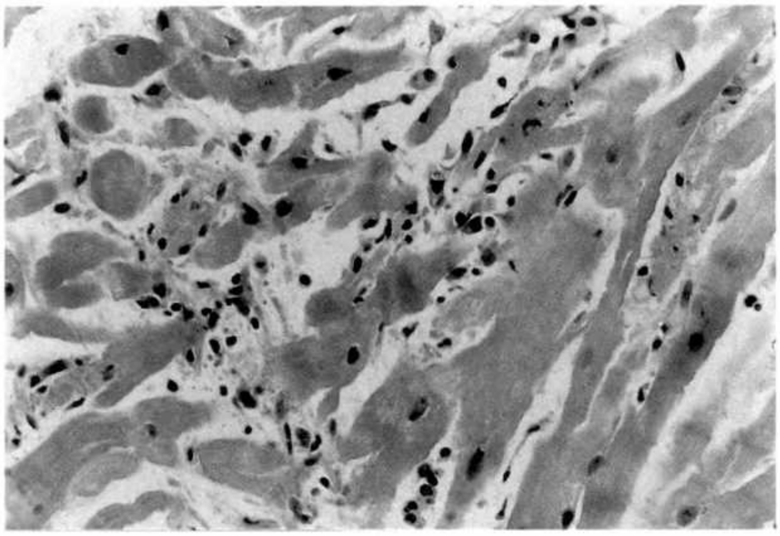
A tenfold increase in the catecholamine concentration in a 24 hour urinary sample confirmed the suspected phaeochromocytoma. A computer tomogram of the abdomen showed a mass of 5·5 × 3·5 cm in diameter in the region of the left adrenal gland. This mass was the only area to show increased uptake of ^{131}I-meta-iodobenzyl-guanidine. The appearance of the endomyocardial biopsy specimen was consistent with a catecholamine-induced cardiomyopathy. One week later treatment with captopril was started and the patient was also given increasing doses of the α antagonist, phenoxybenzamine (up to 60 mg a day). A week later, a radionuclide angiocardiography showed a complete normal myocardial performance and the calculated ejection fraction was 65%.

The phaeochromocytoma was removed one week later without complication. One week after operation the serum and urinary concentrations of catecholamines were within the normal ranges.

Discussion

Acute heart failure caused by a catecholamine-induced cardiomyopathy may be the only symptom of a phaeochromocytoma.[2] Heart enlargement two months before admission suggested the development of cardiomyopathy in our patient. Furthermore, the endomyocardial biopsy findings were consistent with the diagnosis of a catecholamine-induced cardiomyopathy[3] (figure). Treatment with a β blocker rapidly led to pulmonary oedema in our patient, because of unopposed α adrenergic stimulation.[4 5]

Catecholamine-induced cardiomyopathy has been improved or reversed by surgical removal of the catecholamine-secreting tumour or by medical with α blockers over



Endomyocardial biopsy specimen showing fibre necrosis surrounded by infiltrations with monocytes and lymphocytes that is typical of catecholamine-induced cardiomyopathy (haematoxylin and eosin, original magnification, × 350).

several weeks.[6–8] In our patient the clinical signs of congestive heart failure improved within eight hours of treatment with captopril. More important, the abnormally low initial ejection fraction (despite inotropic stimulation) became normal after medical treatment with captopril alone and then when captopril was given in combination with phenoxybenzamine for a total of only two weeks. This increase in the ejection fraction was considerable and overcomes the fact that the two values were measured by two different methods. α Blockade would not have restored cardiac performance in such a short time. We believe therefore that captopril alone or in combination with phenoxybenzamine was responsible for the rapid return to normal of our patient's cardiac performance.

The hypothesis is supported by published experimental data. Hu showed that captopril inhibited the development of the catecholamine-induced cardiomyopathy in rats with phaeochromocytomas.[9] It is unlikely that this effect was the result of captopril's antihypertensive efficacy, because the non-specific vasodilator hydralazine has no effect on the development of catecholamine-induced cardiomyopathy though it normalised blood pressure in the same rats.[10] The difference between captopril and hydralazine can be explained by their different influences on the local cardiac renin-angiotensin system.[11] Angiotensin increases the growth and proliferation rate of myocytes in vitro. Hydralazine activates mycocytological renin activity, which in turn stimulates cardiac hypertrophy. In contrast, captopril inhibits the cardiac renin-angiotensin axis.[11] This is one possible mechanism, by which captopril may counteract catecholamine-induced cardiomyopathy. Furthermore, free radicals from long chain fatty acids, which act as direct myocardial toxins, have been described in phaeochromocytoma.[12] Captopril, an angotensin converting enxyme inhibitor with sulphydryl groups, may be able to scavenge these free radicals.[13]

We thank Dr M Mihatsch, professor of pathology, for the photograph.

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Br Heart J 1992;68:529–30

Delayed complications after myocardial contusion

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Abstract

A 45 year old farmer was kicked in the chest by a horse. In the days following the injury episodic breathlessness developed and he was admitted to hospital with right ventricular failure and pulmonary emboli. Echocardiography showed global right ventricular dysfunction but a right ventricular mural thrombus, the likely source of the pulmonary emboli, was not seen. He gradually recovered after treatment with anticoagulant. One month later he presented with a further complication—complete atrioventricular dissociation—that required a dual chamber pacemaker implantation.

This patient had few initial manifestations of right ventricular myocardial contusion and this case illustrates that such patients should be closely monitored for delayed complications.

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Non-penetrating injuries often cause myocardial contusion, the reported incidence ranges from 8%[1] to 76%[2] and reflects the variable criteria used. Because the right heart is nearer the sternum it is more often affected than the left. Motor vehicle accidents, in particular steering wheel injuries,[3] are the commonest cause. Others include falls from heights, sports accidents, and animal kicks.[4] Myocardial contusion can occur in isolation but it is more frequently associated with multiple injuries. Early complications, often the immediate effects of mechanical dysfunction and tachycardia, usually resolve. However, delayed secondary complications are not only unpredictable but may become life-threatening if unrecognised. This case report illustrates these late problems, which arose despite few clinical signs during the initial presentation.

Case report

A previously fit 45 year old farmer presented to the casualty department of a nearby district general hospital with severe chest pain. He had received a direct blow to the sternum and ribs after being kicked by the hind leg of a horse. Examination showed tenderness and minor superficial skin lacerations in this area. He was haemodynamically stable. Air in the soft tissues was attributed to the skin lacerations. There was a small right basal pleural reaction but chest and rib *x* rays showed no sternal or rib fractures. The skin grazes were cleaned and dressed, and oral dihydrocodeine was prescribed before the patient was discharged.

Two days later he returned to the same casualty department with continuing sternal chest pain, which had not responded to dihydrocodeine, and mild ankle swelling. Despite stronger analgesia his non-cardiac chest pain remained troublesome and in addition he began to experience paroxysms of severe breathlessness. When he re-attended one week later he was dyspnoeic at rest and was admitted. He was pyrexial (38°C) with tachycardia of 140 per minute. The jugular venous pressure was raised to ear level and his blood pressure was 120/70 mm Hg. A gallop rhythm was audible and chest auscultation showed scattered bilateral basal crepitations with reduced left basal air entry. Sacral oedema and gross ankle oedema were present. His blood count was normal apart from a raised white cell count of $14\cdot6 \times 10^9$/l (83% neutrophils). Chest *x* ray showed bilateral basal pleural effusions, a considerable increase in the prominence of hilar vascular shadows and an enlarged cardiac silhouette (though this was not globular). An electrocardiogram showed sinus tachycardia (130 beats per minute), a right bundle branch block pattern, and an inferior infarct pattern. Despite treatment with intravenous diuretic his condition deteriorated. He became hypoxic (Po_2 6·7 kPa in air) and confused, although he remained normotensive (130/70 mm Hg) and did not require inotropic support. At this time he was referred to the regional cardiac unit. A transthoracic echocardiogram showed severe global right ventricular dysfunction, less pronounced in the septal region with no clear evidence of thrombus, and normal left ventricular contractility. No valve or pericardial disease was detected. The patient declined a transoesophageal echocardiogram. Because the clinical picture was suggestive of pulmonary emboli a ventilation/perfusion scan was carried out. It showed multiple bilateral perfusion mismatches. After anticoagulation and with continued intensive treatment over the next 10 days he made a steady recovery and was discharged on warfarin.

At an outpatient clinic one month later he still had moderate breathlessness on exertion and lethargy. There was a bradycardia and an electrocardiogram showed complete nodal atrioventricular block with a ventricular rate of 44 per minute. Before dual chamber pacemaker implantation a transoesophageal

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echocardiogram was performed to look for residual thrombus. This confirmed an improvement in right ventricular contractility but no thrombus was seen. The patient's symptoms improved considerably after pacemaker implantation.

Discussion

In myocardial contusion there are histological changes of myocardial cell necrosis, erythrocyte extravasation, and leucocyte infiltration.[5] Similarities with acute myocardial infarction have been reported[6] and scar tissue formed during healing may account for some of the later complications. The clinical criteria for the diagnosis of myocardial contusion in the acute stage remain uncertain and the importance and significance of the diagnosis has given rise to some controversy.[7] In a retrospective review of 524 patients admitted with suspected myocardial contusion Foil *et al* concluded that in patients with isolated chest wall injury all significant clinical sequelae would become apparent almost immediately after injury.[8] Our case report shows that this is not always so and unrecognised delayed sequelae such as pulmonary emboli or atrioventricular dissociation can be life-threatening. Our patient presented nine days after the injury with a combination of right ventricular dysfunction and recurrent multiple pulmonary emboli caused by right ventricular mural thrombus formation, a well-recognised complication of myocardial contusion. Timberlake and McSwain suggested that echocardiography should assess not only the extent of myocardial injury but should also be targeted to show evidence of mural thrombus.[9] In our patient a transoesophageal echocardiogram was planned but initially declined by the patient.

Although arrhythmias and conduction disturbances are common soon after myocardial contusion these are usually transient and are almost certainly the direct result of injury. Delayed conduction disturbances have not been reported before. Because fibrosis and scar formation are part of the healing process of myocardial contusion,[6] we postulate that in our patient this mechanism was a likely cause for the atrioventricular dissociation that ensued after a few weeks. The block at the nodal level suggests that the fibrotic process affected the septum in the region of the atrioventricular node or the intranodal portion of the common His bundle. Though the untreated course of this process is uncertain there was no reason at this stage to expect resolution and therefore a DDD mode pacemaker was implanted and it resulted in symptomatic improvement.

Even after an apparently trivial injury patients whose mechanism of injury may damage the myocardium should be closely monitored for a wide range of delayed complications that may present insidiously and may result in adverse outcome.

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Br Heart J 1992;68:531–4

AUDIT

Impact of the recommendations of the British Pacing and Electrophysiology Group on pacemaker prescription and on the immediate costs of pacing in the Northern Region

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Abstract

***Background*—The report from the Working Party of the British Pacing and Electrophysiology Group recommends the use of more sophisticated pacemakers in most patients. These proposals were initially circulated in September 1990 and are likely to have major cost implications. Their impact on pacing practice and the immediate costs of pacemaker hardware in the Northern Region were retrospectively audited.**

***Methods*—The pacing records of 550 patients undergoing a first pacemaker insertion at the Freeman Hospital between March 1990 and August 1991 were reviewed. The patient's age, indication for pacing, pacing mode, and the cost of generator and lead(s) were recorded. The cost was compared with the costs of pacing with the optimal and alternative modes recommended by the Working Party. The costs were calculated from the actual mean cost of the recommended unit over the 18 month period of study multiplied by the number of patients who would have received that unit.**

***Results*—96% of patients were paced for sinus node dysfunction, atrioventricular block, or atrioventricular block and atrial fibrillation. The mean (SD) ages of patients in each diagnostic group were: sinus node dysfunction 69·4 (14), sinus node disease and atrioventricular block 67·2 (17·6), atrioventricular block 73·9 (12·5), atrial fibrillation and atrioventricular block 74·0 (13·9), and carotid sinus hypersensitivity 74·6 (11·6) years. Over the 18 month audit period there was an increase in physiological pacing. AAI pacing in patients with sinus node dysfunction increased by 100% and DDD pacing in atrioventricular block increased by 56%. Over the whole 18 month period the adoption of the British Pacing and Electrophysiology Groups optimal recommendations would have increased expenditure on pacemaker hardware in the Northern Region by 94% and the use of the alternative mode would have increased it by 61%. For the last six months alone the excess would be 78% and 48%.**

***Conclusions* The adoption of the recommendations of the British Pacing and Electrophysiology group in the Northern Region would greatly increase the cost of pacing hardware. The greater part of this increase would be attributable to the routine use of dual chamber pacing in patients with atrioventricular block and the increased use of rate responsive units. The benefits of sophisticated pacing in a predominantly elderly population need to outweigh the disadvantages of the increased cost and complexity of follow up.**

(*Br Heart J* 1992;68:531–4)

The complexity and cost of permanent pacing systems for treatment of patients with bradycardias are steadily increasing. Advances in pacemaker technology have led to the availability of more sophisticated units that preserve atrioventricular synchrony and are capable of increasing the rate of impulse generation in response to physical activity. In 1991 the British Pacing and Electrophysiology Group reported the conclusions of a working party on the prescription of pacemakers for symptomatic bradycardia.[1] This paper recommends the use of more sophisticated pacemakers in most patients. This is likely to entail a major change in the practice of most British

Table 1 Recommended optimal and alternative pacing modes

	Optimal	*Alternative*
SND	AAIR	AAI
AVB	DDD	VDD
SND + AVB	DDDR	DDD
	DDIR	DDI
AVB + AF	VVIR	VVI
CSS/MVVS	DDI	—

SND, sinus node dysfunction; AVB, atrioventricular block; AF, atrial fibrillation or flutter; CSS, carotid sinus syndrome; MVVS, malignant vasovagal syncope.

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Table 2 Indications for pacemaker insertion

Diagnosis	*Period* 1	2	3	*Overall (%)*
SND	34	53	61	148 (27)
SND+AVB	2	3	1	6 (1)
AVB	106	98	125	329 (60)
AVB+AF	19	15	18	52 (9)
CSS	2	2	11	15 (3)

SND, sinus node dysfunction; SND+AVB, sinus node dysfunction and atrioventricular bloc AVB, atrioventricular block; AVB+AF, atrioventricular block and atrial fibrillation/flutter; CS carotid sinus syndrome.

pacemaker centres and has considerable financial implications, both in terms of the initial outlay on pacing hardware and the more complex follow up that is required.

We audited pacing practice in the Northern Region to determine both the change in practice since the initial circulation of the findings of the working party in September 1990 and the effect of its recommendations on expenditure on pacing hardware.

Patients and methods

We examined the records of all patients undergoing a first implantation of a permanent pacing system in the Northern Regional Cardiothoracic Centre at the Freeman Hospital, Newcastle, from March 1990 to August 1991. This is the only centre for implanting permanent pacemakers in the Northern Region, which has a population of approximately three million. The age, indication for pacing, pacing mode, and the cost of the pacing generator and lead were recorded. The costings used were those current in August 1991 and were exclusive of value added tax. Individual costs included the cost of any replacement lead or generator that had to be inserted in the month after the initial procedure. Patients were grouped according to the time of pacemaker insertion: for period 1, 1 March 1990 to 31 August 1990; period 2, 1 September 1990 to 28 February 1991; period 3, 1 March 1991 to 31 August 1991. The costs of pacing with the optimal and alternative modes recommended by the Working Party were derived by taking the actual mean cost of the recommended unit over the 18 month period of the study and multiplying it by the number of patients who would have received that unit had the recommendations been followed. Unlike the true costs, these derived costs assume that no generator or lead had to be replaced. Table 1 shows the optimal and alternative pacing modes recommended by the British Pacing and Electrophysiology Group. The regional pacing service does not stock dedicated VDD units so DDD units were used instead. Data are expressed as mean (SD).

Results

Over the 18 month study period 550 new patients had pacemakers inserted. Table 2 shows the distribution of these patients by diagnosis in each six month period. In nearly all of them (96%) a pacemaker was inserted for sinus node dysfunction, atrioventricular block, or atrioventricular block with atrial fibrillation. The proportion of patients with each diagnosis remained more or less constant over the three periods except for a fivefold increase in the number with carotid sinus hypersensitivity in the last period. The mean ages of the patients in each diagnostic group were: sinus node dysfunction 69·4 (14) years, sinus node disease and atrioventricular block 67·2 (17·6) years, atrioventricular block 73·9 (12·5) years, atrial fibrillation and atrioventricular block 74 (13·9) years, and carotid sinus hypersensitivity 74·6 (11·6) years. Table 3 shows the type of pacing unit inserted for each diagnosis in each six month period. Two patients with carotid sinus hypersensitivity received an inappropriate AAI pacemaker.

During the first period 70·6% of patients with sinus node dysfunction received a VVI unit compared with 47·1% in period 2 and 41% in period 3. In contrast AAI units were inserted in 14·7% in period 1, 30·2% in period 2, and 31·1% in period 3. The atrium was paced either alone or in combination with the ventricle in 24% in period 1, 52% in period 2, and 59% in period 3. Patients receiving VVI units were on average 5–10 years older than those in whom the atrium was paced.

A high proportion of patients with atrioventricular block were paced with VVI units. Use of DDD pacemakers increased from 12·3% in period 1 to 19·2% in period 3. Only a small proportion of patients were paced VVIR

Table 3 Percentages of patients in each diagnostic group paced with each mode in each period

Period	*VVI*	*VVIR*	*AAI*	*AAIR*	*DDD*	*DDDR*	*DDI*	*All**
SND: 1	70·6	5·9	14·7	—	2·9	5·9	—	34
2	47·1	—	30·2	5·7	15·1	1·9	—	53
3	41·0	—	31·1	8·2	11·5	1·6	—	61
SND+AVB: 1	50·0	—	—	—	50·0	—	—	2
2	66·7	—	—	—	—	33·3	—	3
3	—	—	—	—	100·0	—	—	1
AVB: 1	83·0	3·8	—	—	12·3	0·9	—	106
2	81·6	3·1	—	—	15·3	—	—	98
3	76·0	4·8	—	—	19·2	—	—	125
AVB+AF: 1	89·5	10·5	—	—	—	—	—	19
2	93·3	6·7	—	—	—	—	—	15
3	77·8	22·2	—	—	—	—	—	18
CSS: 1	100·0	—	—	—	—	—	—	2
2	—	—	50·0	—	50·0	—	—	2
3	9·1	—	9·1	—	9·1	—	72·7	11

SND, sinus node disease: SND+AVB, sinus node disease plus atrioventricular block; AVB; atrioventricular block; AVB+AF, atrioventricular block plus atrial fibrillation/flutter; CSS, carotid sinus syndrome.
*Total number of patients in each diagnostic group at each time.

Table 4 Mean (SD) cost for each pacing mode over the 18 month period

Mode	*Cost (£)*
VVI	631 (165)
VVIR	1773 (416)
AAI	927 (317)
AAIR	1642 (198)
DDD	1811 (255)
DDDR	1992 (255)
DDI	1845 (117)

and only one patient received a DDDR unit. Patients paced VVI were substantially older than those paced with more complex units. Similarly, most patients with combined atrial fibrillation and atrioventricular block were paced VVI, with VVIR units being used selectively in younger and more active patients.

Table 4 shows the mean cost of each mode of pacing over the 18 month period. Table 5 shows the actual mean cost of pacing for each diagnosis in each of the three time periods compared with the mean cost of following the British Pacing and Electrophysiology Groups optimal and alternative recommendations. The actual mean (SD) cost of hardware per patient increased from the first to the last period from £844 (433) to £1050 (476) for sinus node disease (25%), from £822 (554) to £913 (509) for atrioventricular block (11%), and from £727 (320) to £895 (519) for atrioventricular block and atrial fibrillation (23%). The mean costs of pacing sinus node dysfunction with atrioventricular block in period 1 and carotid sinus syndrome in period 3 are very high. There were only two patients in each of these groups and in each case one of the patients required a replacement generator, which considerably increased the mean cost. Over the 18 month period the adoption of the recommended optimal pacing practice would have increased the budget for pacing hardware by 94% and the use of the alternative units would have increased it by 61%. This would have increased the annual pacing budget from £333 535 to £647 163 for the optimal mode and to £536 289 for the alternative mode. By far the greater part of this excess would arise from the routine use of dual chamber pacemakers in patients with atrioventricular block. Pacing policy at the Freeman Hospital has clearly evolved in response to the recommendations and, if only period 3 is taken into account, the overall cost impact is less pronounced—an increase of 78% for the optimal mode and 48% for the alternative. This would result in an increase from £427 401 to £760 801 per year for the optimal mode and to £632 075 per year for the alternative mode.

Discussion

The report of the British Pacing and Electrophysiology Group on pacemaker prescription for symptomatic bradycardia proposes profound changes in pacemaker practice.[1] In response to these recommendations, which were initially circulated in September 1990, there were considerable changes in regional pacing practice. These changes resulted in an increase in the cost per patient for pacing hardware but the full implementation of the British Pacing and Electrophysiology Groups recommendations would result in a further substantial increase in expenditure.

Table 5 Actual mean (SD) costs (£) of pacing hardware for each diagnosis in each time period and calculated costs for the BPEG optimal and alternative recommendations

Diagnosis	*FRH 1*	*FRH 2*	*FRH 3*	*BPEG 1*	*BPEG 2*
SND	844 (433)	969 (510)	1050 (476)	1642	927
SND+AVB	2308 (484)	1142 (726)	1865	1992	1811
AVB	821 (554)	839 (491)	913 (509)	1811	1811
AVB+AF	726 (320)	657 (226)	895 (519)	1773	631
CSS	530 (28)	2260 (389)	1592 (441)	1811	1811

FRH 1, 2, and 3, Freeman Hospital periods 1, 2, and 3; BPEG 1, optimal recommendations of the British Pacing and Electrophysiology Group; BPEG 2, alternative recommendations of the British Pacing and Electrophysiology Group; SND, sinus node disease; SND+AVB, sinus node disease and atrioventricular block; AVB, atrioventricular block; AVB+AF, atrioventricular block and atrial fibrillation; CSS, carotid sinus syndrome.

The major changes in pacing practice within the Northern Region have been for sinus node dysfunction where the use of atrial pacing more than doubled. There is general agreement on the advantages of atrial pacing in patients with sinus node dysfunction. It reduces the incidence of atrial fibrillation, systemic embolism, and heart failure and may prolong life.[2 3] Previously, most patients with sinus node dysfunction received a VVI unit. The cost of switching from VVI to AAI pacing is relatively small but the widespread use of rate responsive atrial pacing or of dual chamber pacing in patients with sinus node dysfunction would add considerable expense. Current practice in the Northern Region is to implant rate responsive units only where chronotropic incompetence is considered likely to be an important symptomatic limiting factor—that is, in those patients who are otherwise active and mobile.

Many patients with sinus node dysfunction were paced with single chamber ventricular units even in the last six months of the audit. To some extent this is probably a continuation of previous pacing practice. There is, however, a case for the use of VVI units in very immobile elderly patients with intermittent or vague symptoms, when there are doubts about the presence of atrioventricular conduction abnormalities and where dual chamber pacing would be the only alternative.

The general adoption of dual chamber pacing in patients with atrioventricular block would add considerably to pacing costs in the Northern Region. Maintenance of atrioventricular synchrony in patients with atrioventricular block improved effort tolerance and subjective variables such as breathlessness, palpitation, and general wellbeing.[4] On this basis dual chamber pacing is clearly indicated in more active patients, who are likely to be younger. In patients with limited mobility, particularly the elderly, other factors must be taken into account and the potential benefits of physiological pacing weighed against the disadvantages. In the Northern Region only the Freeman Hospital has the necessary equipment and technical expertise to deal with complex pacemakers. Therefore any patient with a complex unit has to be followed up in Newcastle, which may entail considerable inconvenience, particularly for elderly or infirm patients, who in some cases may be faced with a round trip of over 200 miles. Another factor that must be taken into account is the increase in procedure time and the small increase in procedural complications associated with dual chamber pacing.[5]

This audit has considered only the immediate costs of changes in pacing policy. Many other factors such as increased technician training, increased complexity of follow up, and "quality of life" measures are important long term. Regional pacing practice in the Northern Region has changed in response to the recommendations of the British Pacing and Electrophysiology group. The major change has been where the cost is least—atrial pacing for sinus node dysfunction. Implementation of the full proposals for DDD and rate responsive pacing would considerably increase expenditure on pacing hardware. In a cash limited service the potential benefit of a suggested change in treatment must be weighed against the extra expense and inconvenience.

1 Report of a working party of the British Pacing and Electrophysiology Group. Recommendations for pacemaker prescription for symptomatic bradycardia. *Br Heart J* 1991;66:185–91.
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4 Perrins JE, Morley CA, Chan SL, Sutton R. Randomised controlled trial of physiological and ventricular pacing. *Br Heart J* 1983;50:112–7.
5 Sutton R, Ingram A, Briers L, *et al.* Ten years of physiological cardiac pacing. In: Belhassen B, Feldman S, Copperman Y, eds. Cardiac pacing and electrophysiology. Jerusalem: R&L Creative Communications, 1987:141–2.

Correction

Coronary venous lipid peroxide concentrations after coronary angioplasty: correlation with biochemical and electrocardiographic evidence of myocardial ischaemia. *K G Oldroyd, J R Paterson, A G Rumley, H Eteiba, A P Rae, J Shepherd, S M Cobbe, I Hutton* (July issue, volume 68: pages 43–7.) There were several editorial mistakes in figure 3 of this paper, for which we apologise. A correct version is shown on the right.

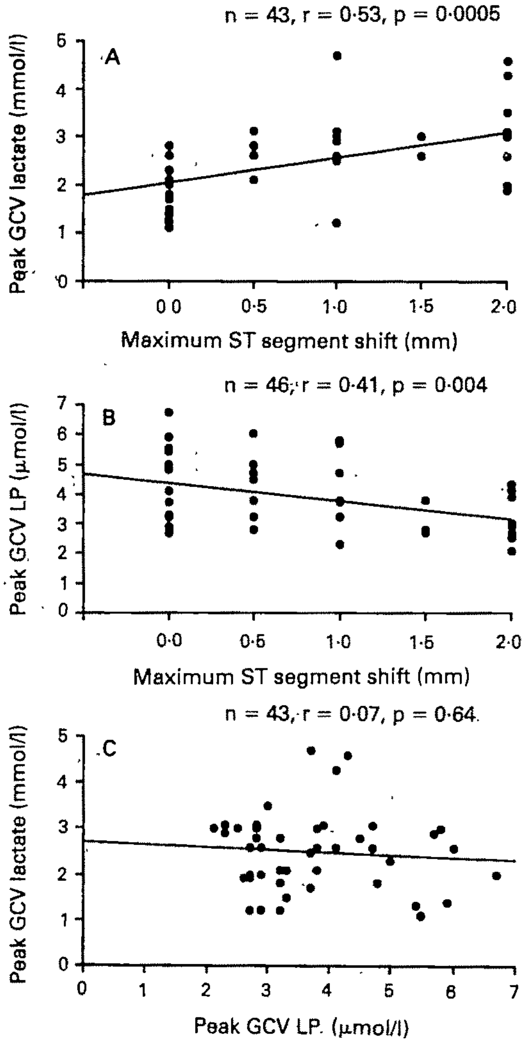

Figure 3 Simple linear regression analysis of the relation between (A) peak lactate concentration in the great cardiac vein (GCV) and maximum ST segment shift; (B) peak GCV lipid peroxide (LP) concentration and maximum ST segment shift; (C) peak GCV lactate concentration and LP concentration.

Essential reading

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EDITED BY RICHARD SMITH, EDITOR OF THE BMJ

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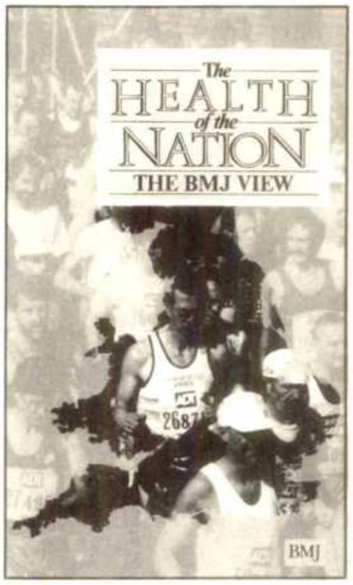

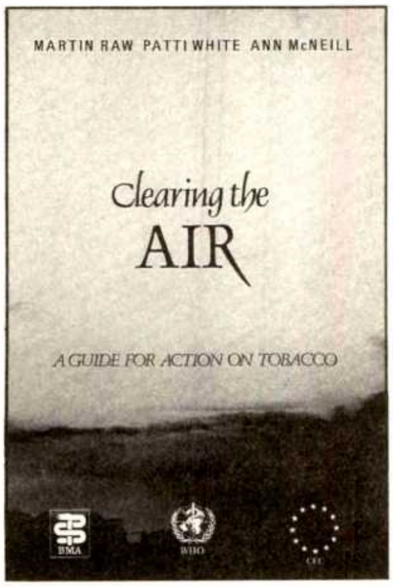
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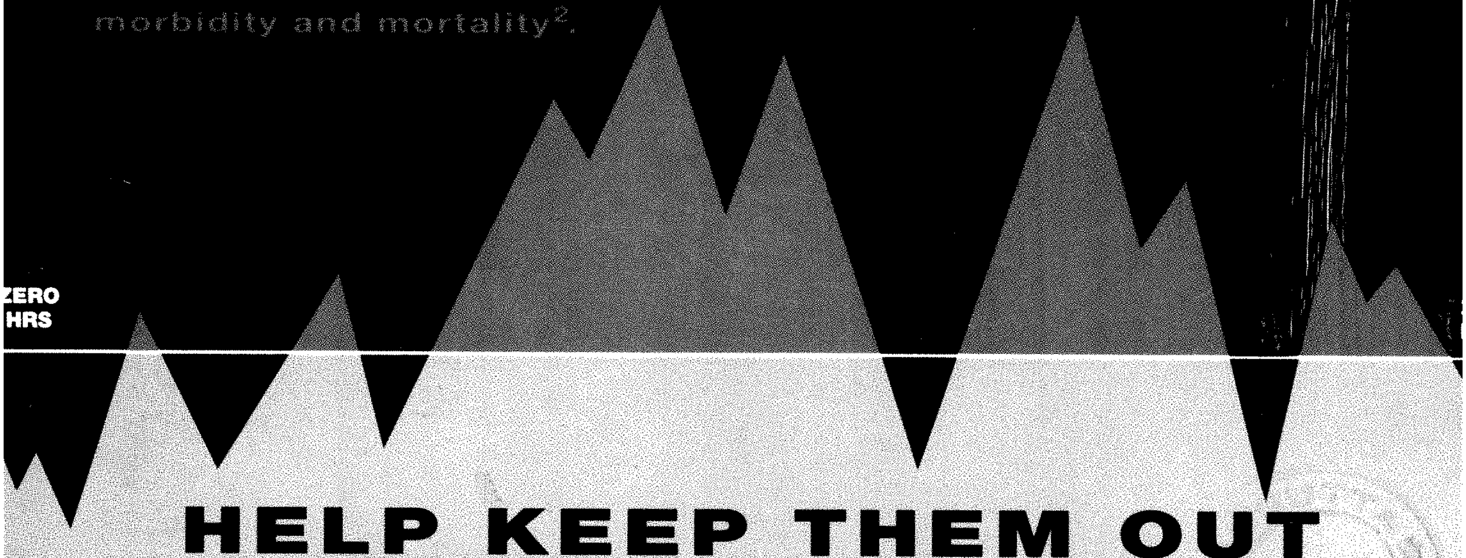

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REFERENCE: 1. Kannel WB. Am J Med 1983; **75:** 4-11.

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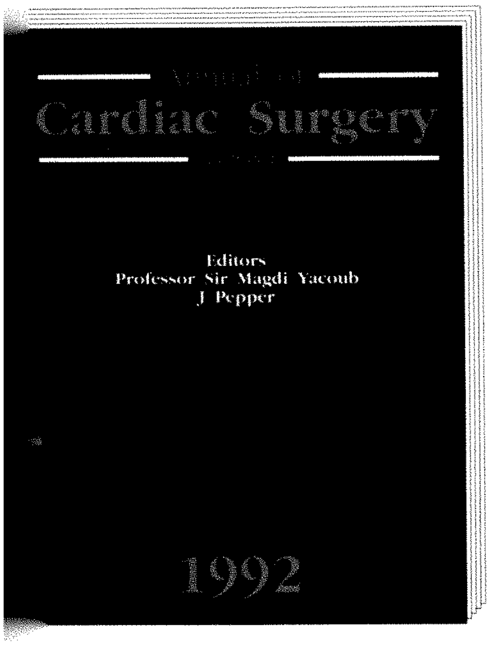
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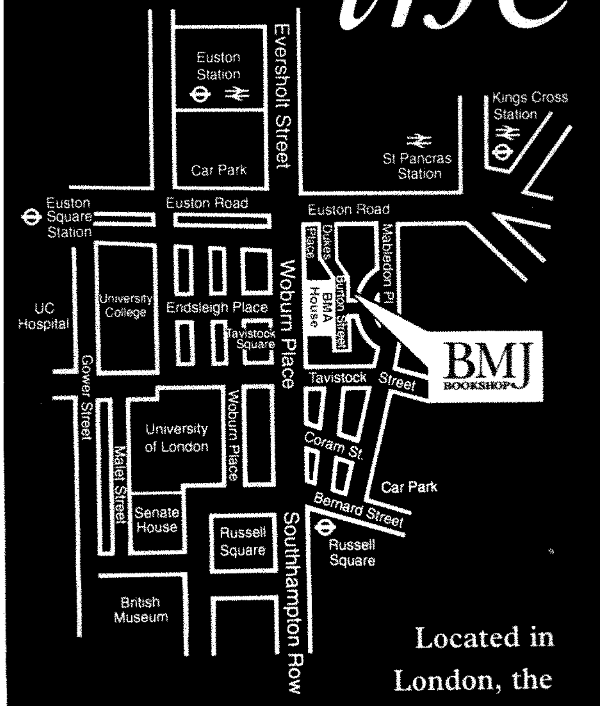

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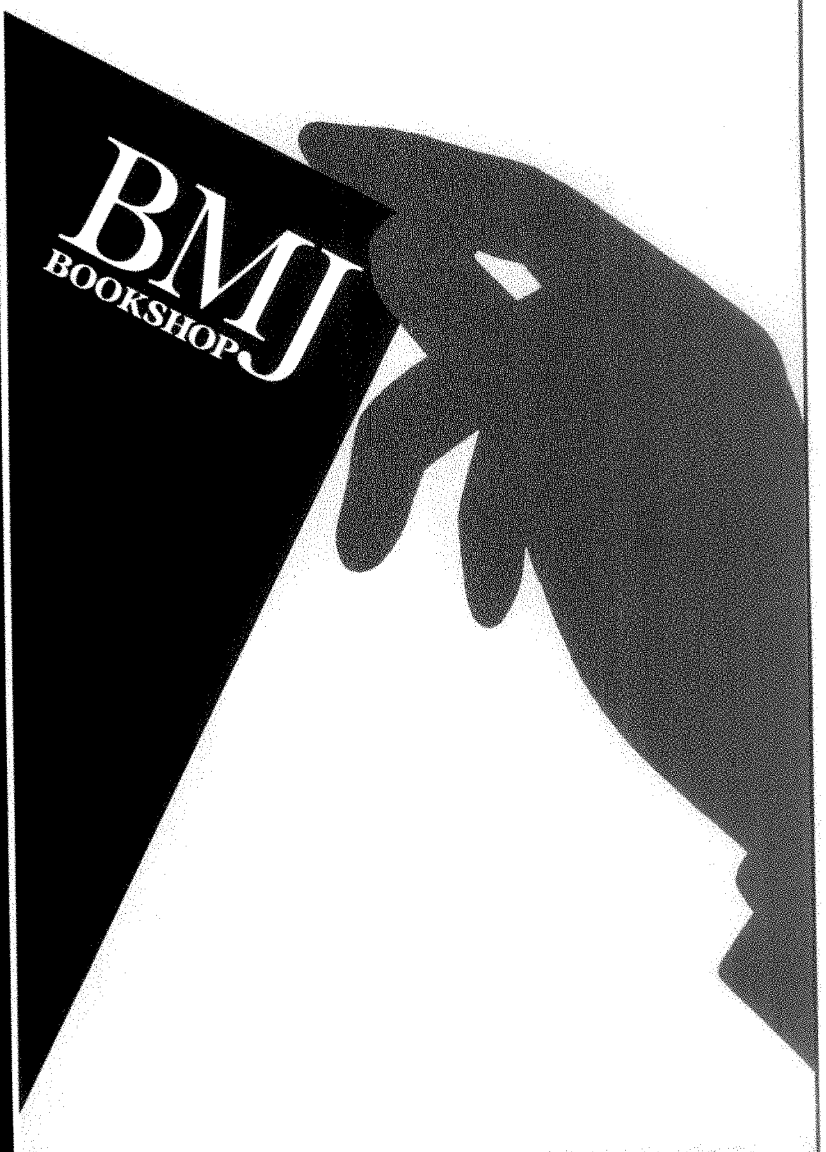

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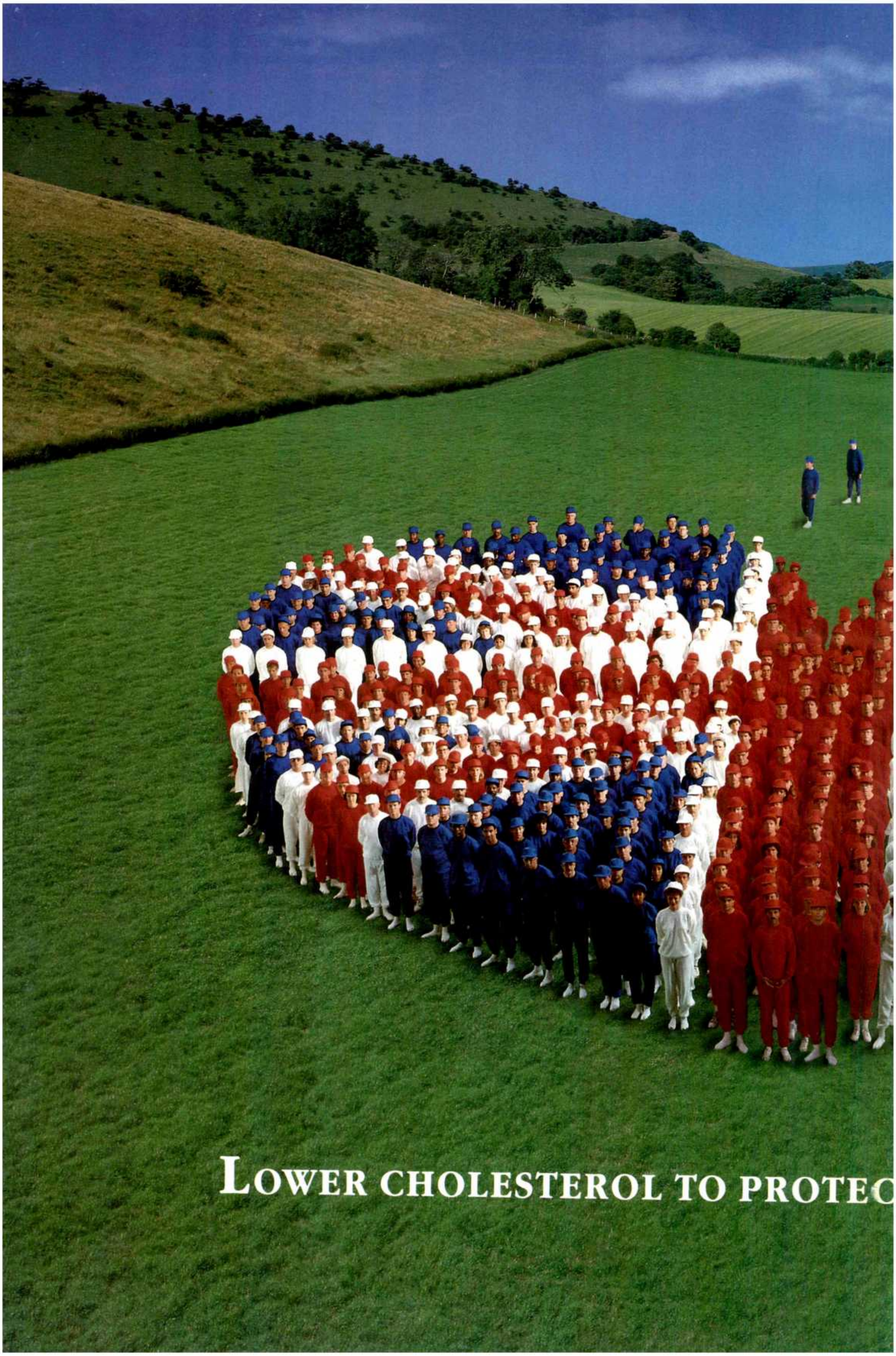
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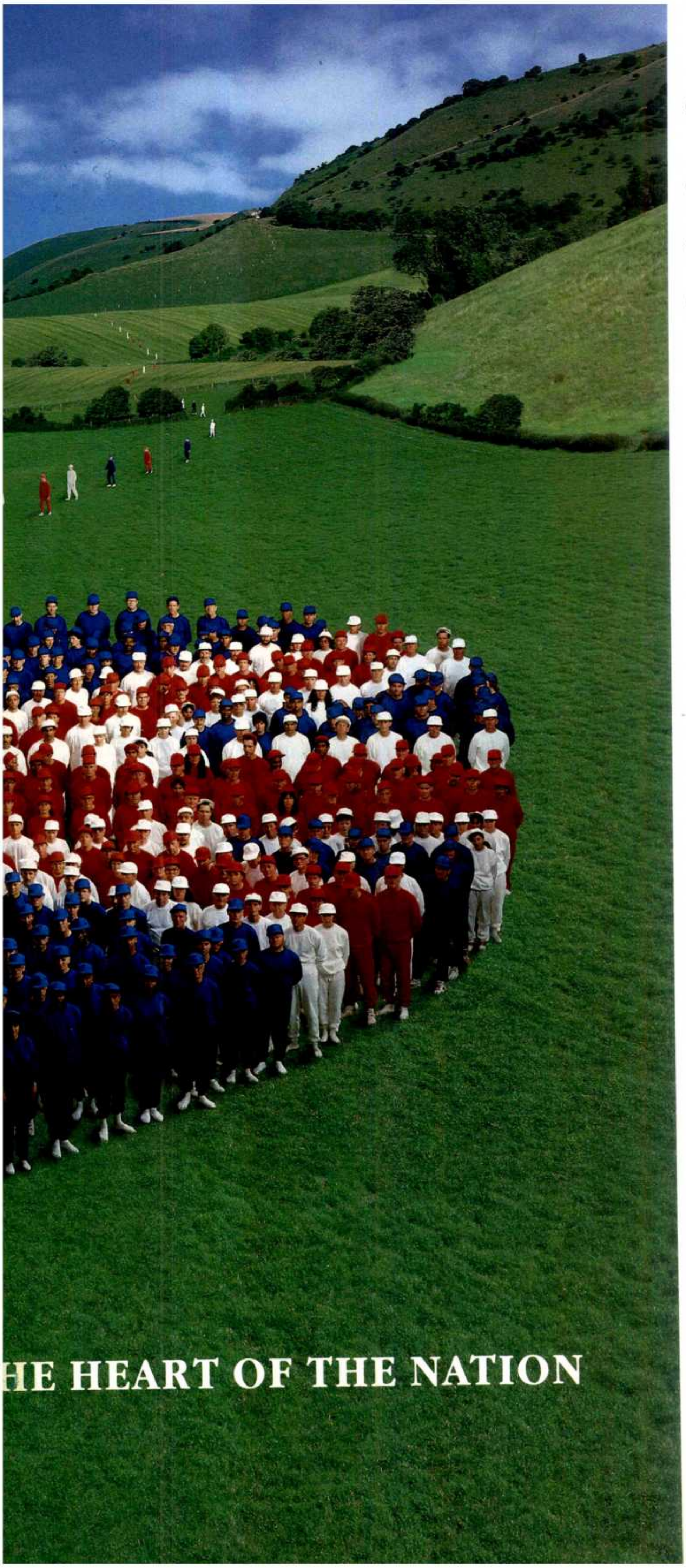
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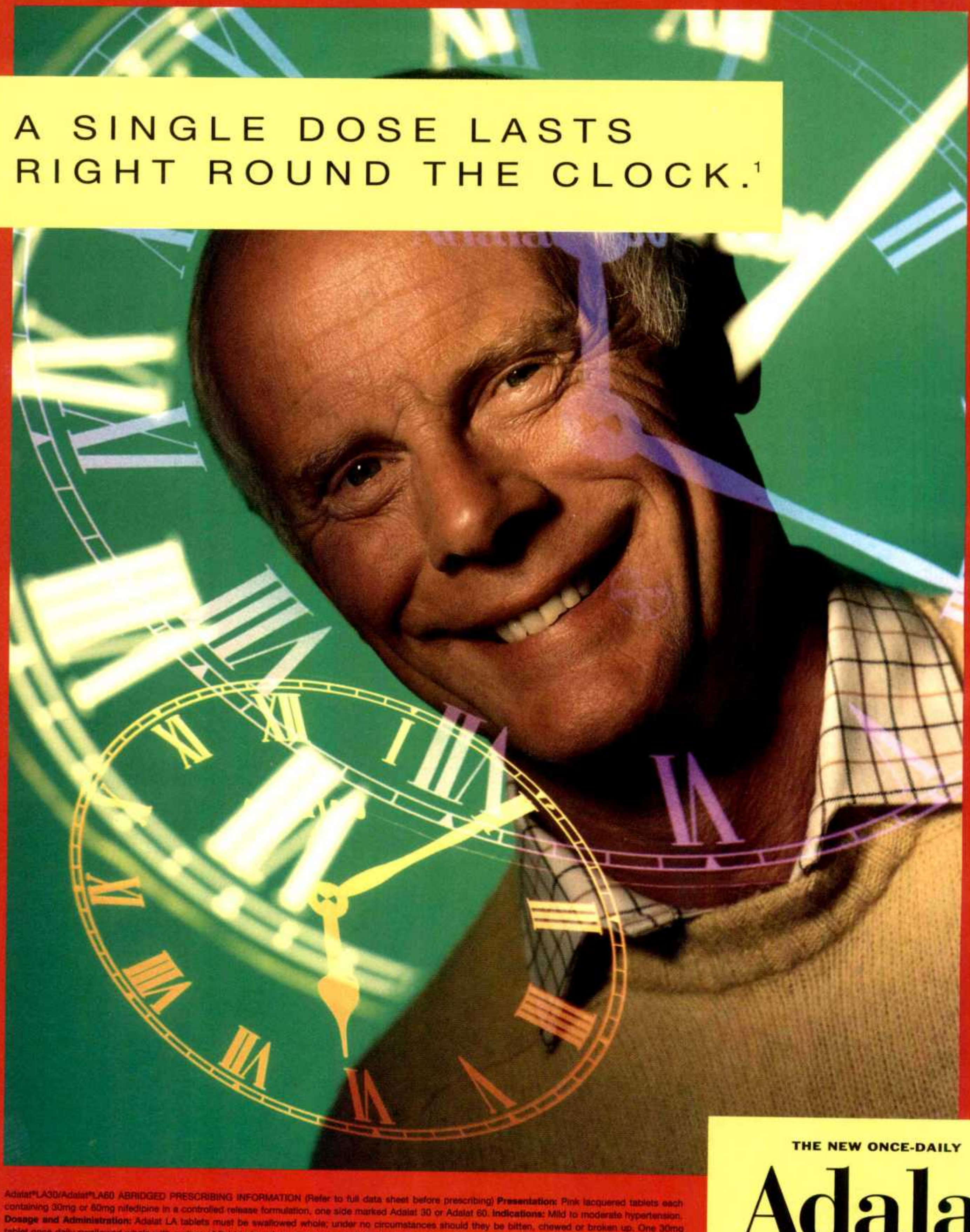
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Editorial

Viable myocardium and reinjection of thallium

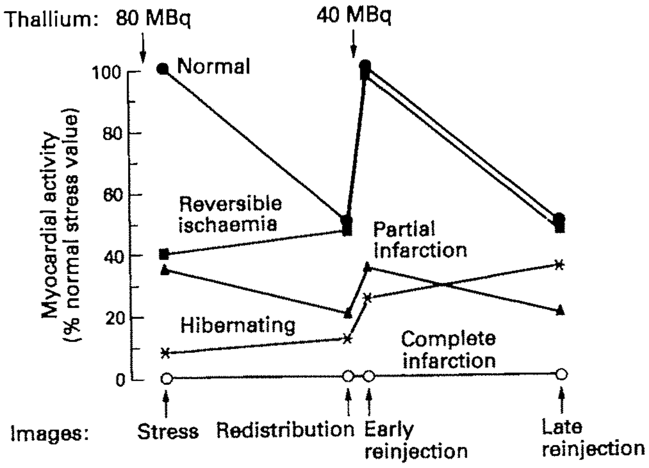
Symptoms and prognosis in patients with coronary artery disease are related to the presence and extent of abnormal myocardial perfusion. The most successful methods of assessing perfusion directly use radioactive tracers such as thallium-201, cationic complexes of technetium-99m, and positron emitters such as rubidium-82 and ^{13} N-ammonia. All of these radiopharmaceuticals rely on the principle that the initial tissue distribution of a tracer that is efficiently extracted from the blood reflects delivery of tracer and hence perfusion.[1] The use of thallium has matured since its first description 17 years ago[2] and it now routinely provides diagnostic[3] and prognostic information.[4] It is superior to other non-invasive tests for the detection,[5] localisation,[6] and grading of coronary artery disease,[7] and its ability to assess the extent of myocardial jeopardy makes it a predictor of future cardiac events[8] at least equal in power to coronary arteriography.[7,9–11] The functional information provided by thallium complements the anatomical information provided by arteriography, and the distinction between the two means that a complete assessment of the patient with coronary disease often requires both types of information.

Early studies used two separate injections of thallium to compare exercise and resting perfusion, but this was abandoned when it was discovered that images acquired several hours after a stress injection were similar to those that would have been obtained had the thallium been injected at rest.[12,13] Such redistribution is the result of the equilibration between intracellular and extracellular thallium and it allows the reversibly ischaemic myocardium to make good the reduced delivery during stress by extracting thallium from the small amount remaining in the blood pool once relatively homogeneous resting perfusion is restored. Thus conventional interpretation of stress and redistribution thallium images equates a reversible defect with myocardium that is normally perfused at rest but ischaemic during stress, a severe and fixed defect with the absence of viable myocardium, and a mild but fixed defect with a mixture of scar and viable myocardium.

This all seemed satisfactory until the introduction of positron emission tomography and tracers such as ^{18}F-fluorodeoxyglucose (FDG), which allowed the assessment of myocardial metabolism and showed that conventional stress and redistribution thallium imaging underestimated the presence of metabolically active myocardium. In 1986 Tillisch and colleagues showed that myocardium with impaired function, reduced perfusion, but increased glucose metabolism was capable of recovering mechanical function after restoration of blood flow.[14] Such areas are now commonly referred to as "hibernating".[15] The next year the same group compared conventional stress and redistibution thallium imaging with FDG imaging and showed that glucose metabolism (and hence presumably viable myocardium) was present in 58% of segments with a fixed thallium defect.[16] Other studies that had cast doubt on the equation of a fixed defect with irreversible myocardial injury included pathological studies[17] and the fact that uptake could improve in fixed defects after angioplasty[18] and bypass grafting.[19] Thus the reliance on a perfusion marker alone for the assessment of myocardial viability risked underestimation of the extent of salvageable tissue.

Used appropriately, however, thallium is more than a perfusion marker because the completed redistribution pattern provides an image of viable myocardium unmodified by differences of perfusion between territories (figure). In this respect thallium differs from most other perfusion tracers which either do not redistribute (^{99m}Tc-methoxy-isobutyl-isonitrile)[20] or which have such short half lives that imaging of a redistribution pattern is impossible (^{87}Rb). The distinction between early (perfusion) and late (viability) thallium images has been known for many years[21–23] although only more recently have its full implications for the detection of hibernating myocardium been appreciated. One problem is that redistribution can be a slow process and conventional four hour images may not provide reliable information. In one study that compared 4 and 24 hour redistribution imaging, the later images showed reversibility in 64% of defects that were irreversible at 4 hours.[24] Ninety five percent of these reversible segments showed improved thallium uptake after revascularisation compared with 37% of the fixed defects. The rate of redistribution seems to be related to the rate of perfusion because myocardium that is subtended by occluded or tightly stenosed arteries has particularly slow redistribution.[25,26]

Unfortunately, late imaging gives low count rates and poor images and an obvious alternative is to give a second injection of thallium at rest.[27,28] Dilsizian and colleagues acquired conventional redistribution images three to four hours after stress injection of 74 MBq of thallium, and they then gave a further 37 MBq at rest. Approximately half of the segments with fixed defects at three hours had improved uptake after reinjection.[27] In 20 of their 100 patients who subsequently underwent coronary angioplasty 13 (87%) of 15 regions identified as viable by reinjection had normal uptake and improved wall motion after the intervention, and none of the eight regions with fixed defects on reinjection imaging had any improvement in uptake or wall motion. Images acquired in this way are an amalgamation of the redistributed initial injection and the pattern of the resting injection. The resting injection will initially distribute itself according to resting perfusion and so a territory with stress-induced ischaemia and slow redistribution will appear to improve because of equal delivery of thallium to the normal territory and to the affected territory at rest. In theory, a territory with viable



Myocardial thallium activity in four different types of myocardial abnormality compared with normal uptake immediately after stress, after redistribution, immediately after reinjection of thallium at rest, and after a further period of redistribution. Uptake is expressed as a percentage of the normal uptake immediately after stress, although the appearance of a defect depends upon the ratio between normal and abnormal myocardium at any one time. Reversibly ischaemic myocardium shows total redistribution even before reinjection. Partial thickness and complete infarction show a fixed defect which is either partial or complete. Viable myocardium with poor resting flow (potentially hibernating) shows a slow early increase in uptake, an increase after reinjection, and a further increase with later redistribution. Hence the redistribution may not be visually apparent until after reinjection.

myocardium but reduced resting perfusion will still show a defect immediately after resting injection, but further redistribution will equalise the uptake in viable myocytes irrespective of perfusion. This suggests that the reinjection images should not be acquired immediately after reinjection but after another period of redistribution.[29 30] In practice, immediate imaging may be sufficient. Dilsizian and colleagues studied a further 50 patients with chronic stable angina and showed that 23 of 25 segments with improved uptake immediately after reinjection showed no further improvement 24 hours later and that 29 of 30 segments with fixed defects immediately after reinjection remained fixed 24 hours later.[31]

Two practical implications of reinjection should be considered. First, uncertainty about the need for an additional dose of thallium and the extra imaging time required can play havoc with a busy clinical schedule, not to mention the departmental budget. Second, 40 MBq of thallium after an initial injection of 80 MBq will exceed the maximum dose recommended in the United Kingdom by the Administration of Radioactive Substances Advisory Committee (ARSAC), although not that commonly given in other countries. Specific approval should therefore be sought for such a protocol.

Given what we now know, can positron emission tomography still justify its main clinical indication, which is for the assessment of myocardial viability using FDG? When Bonow and colleagues compared thallium reinjection with DGG images they found FDG uptake in 91%, 84%, and 51% of segments which had mild, moderate and severe fixed thallium defects after four hour redistribution imaging.[32] Thus only for the severe fixed defects was conventional thallium imaging inadequate. Reinjection of thallium showed viable myocardium in 51% of the severe fixed defects and there was 88% concordance between FDG imaging and thallium reinjection. Tamaki and colleagues have also compared the two and have shown that 65% of segments with viable myocardium predicted by thallium had improved function after bypass grafting but only 25% of segments judged to be nonviable by thallium had improved function.[33] Thus there is broad agreement between thallium reinjection and FDG imaging, and whether the superior imaging characteristics of positron emitters will make any difference in clinical practice remains to be seen.

And what of alternative methods of detecting hibernating myocardium that do not rely on radioactive tracers? Bear in mind that the different metabolic and mechanical functions of the cardiac myocyte may not be damaged and recover in parallel and that in practical terms the most important aspect of viability is recovery of mechanical function after intervention. The response of myocardial motion and thickening to inotropic challenge may therefore be important. Echocardiography has shown that the ability of a region to improve systolic wall thickening in response to dobutamine stress predicts an improvement of abnormal resting function after revascularisation.[34] However, because myocardial thickening can deteriorate with dobutamine induced ischaemia,[35] the full story is unlikely to be told without a knowledge of perfusion as well as of contractile function.

What therefore can we conclude about the routine use of thallium in patients with coronary artery disease? Certainly, conventional imaging with stress and 2–4 hour redistribution imaging should continue unchanged for the detection and assessment of coronary artery disease. Such a policy will answer most questions posed by myocardial perfusion imaging in patients with stable coronary artery disease. Even if redistribution is incomplete at four hours, later imaging or reinjection will not provide additional information. If, however, it is important to know whether there is viable myocardium within an area of absent uptake, than a further injection will answer the question with reasonable confidence. Such a question might arise if the scan shows no other area of reversible ischaemia in a patient with previous infarction and recurrent angina, or in a patient with ischaemic heart failure in whom revascularisation is being considered to improve ventricular function as much as to relieve angina. The ability to detect hibernating myocardium in this way widens the indications for thallium imaging and highlights the importance of the assessment of myocardial perfusion and viability in complementing the knowledge of coronary anatomy provided by invasive investigation.

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REVIEW

Adaptation of the maternal heart in pregnancy

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Major adaptations occur in the maternal cardiovascular system during normal pregnancy and knowledge of these changes is essential to the management of women with cardiovascular disease. Cardiac output increases during pregnancy but the extent and timing of this increase and the underlying causes have been a subject of debate. The controversy was largely the result of differences in investigative techniques and the design of the clinical studies. From the earliest work, of Linhard in 1915,[1] to the present day, investigators have vacillated between the repeatability but inaccuracy of indirect Fick methods and the potential hazards and ethical problems of longitudinal invasive investigations by dye dilution or the direct Fick method. As a result many early studies were cross sectional in design and therefore limited by the wide variations in cardiac output and stroke volume between individuals.

The non-invasive techniques of M mode echocardiography and impedance echocardiography were first used in the 1960s and 1970s. Cardiac output could be measured serially without risk or discomfort to the subject. Such techniques allowed the design of studies in which each woman acted as her own pre-pregnant control. Determination of cardiac output by impedance cardiography was described by Kubicek *et al* in 1966.[2] This technique used changes in transthoracic electrical resistance resulting from ejection of blood into the pulmonary circulation. A comparison with thermodilution measurements during caesarean section[3] showed a poor correlation with impedance cardiography. de Swiet and Talbert subsequently cast considerable doubt on the assumptions of the Kubicek technique[4]: the validity of the results obtained with it have subsequently been questioned. On the other hand M mode echocardiography did seem to have some merit for longitudinal pregnancy studies. Stroke volume was calculated by cubing the minor left ventricular internal dimensions.[5] This method assumed that the left ventricle was an ellipsoid of revolution (rugby ball shaped) so that the long axis was twice the minor axes. When ventricular function and structure are normal this method seems to be valid. However, Fortuin *et al* showed that dilatation of the left ventricle destroys the essential mathematical relation and with it the validity of the method.[6] During pregnancy heart volume and end diastolic dimension do both increase progressively[7,8] and therefore the M mode "cubing method" may not be valid.

Echo Doppler methods

The product of flow velocities recorded by pulsed or continuous wave Doppler ultrasound with cross sectional area measured from cross sectional images is an accepted way of calculating stroke volume and cardiac output. There are several technical variations and the inherent assumptions are well reviewed by Goldberg *et al*.[9] Since 1987 the technique has been used for a series of studies of the normal maternal heart during pregnancy in our department.[10] In our early validatory studies cardiac output was calculated from the pulmonary, mitral, and aortic valves, which allowed us a "within patient" control for the values recorded. We initially validated these results from the aortic, pulmonary, and mitral valves against simultaneous direct Fick measurements. The correlation was good and the limits of agreement were ± 0·8 l/min.[10] We also studied within patient, intraobserver, and chronological coefficients of variation for the measurements. These were all equal to or less than 5% for each of the three sites studied. The technique was then applied systematically to several serial studies of cardiac output in pregnant subjects. The results form the basis for the summary of haemodynamic changes that follows.

Haemodynamic changes during normal singleton pregnancy

Our initial longitudinal studies of cardiac output started before conception and continued through to the postnatal period. Because of the effect on cardiac output of the supine position, which leads to caval occlusion by the gravid uterus,[11] throughout all the studies measurements were performed in the left half lateral position.

Cardiac output had increased by five weeks after the last menstrual period and the increase continued to 24 weeks when it was 45% above the non-pregnant level (fig 1). Thereafter no further significant change was found. Both heart rate and stroke volume contributed to this increase: the heart rate increase was seen by five weeks' gestation and continued till 32 weeks. The stroke volume increase occurred a little later at eight weeks and reached its maximum at

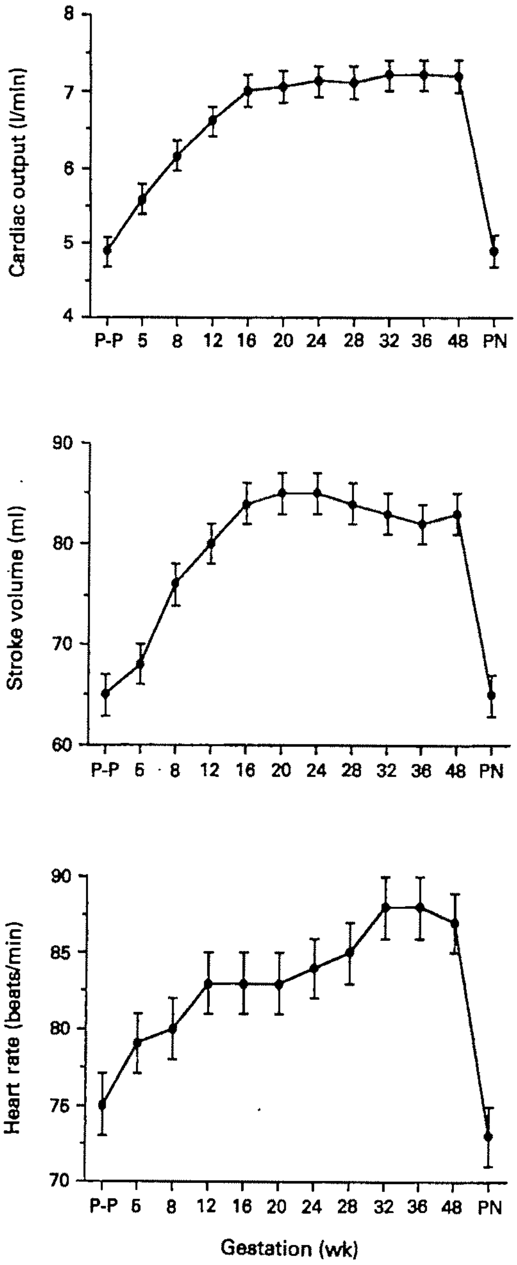

Figure 1 Increase in cardiac output from the non-pregnancy state throughout pregnancy. P-P, pre-pregnancy; PN, postnatal.

about 20 weeks. There was a slight fall in stroke volume after 38 weeks but this was not significant. However, other workers reported a fall in stroke volume in the last month of pregnancy.[12]

These results suggest that cardiac output increases earlier than previously reported. Cardiac output reached a maximum at the end of the second trimester. The maximum values and the time at which they were achieved resembled other reports.[8 12–15]Similarly the reduction in cardiac output after pregnancy is similar to the 43% reduction reported by Clark *et al* in 1989.[16]

Haemodynamic changes during twin pregnancy

We had the opportunity to carry out a serial study of haemodynamic function during twin pregnancy.[17] Cardiac output was on average 15% higher throughout pregnancy compared with singleton pregnancy. This increase was due to a relatively greater increase in heart rate and was associated with a significantly larger increase in left atrial diameter representing increased volume overload.

Haemodynamic changes in labour

Previous studies of the haemodynamic changes during labour had suggested that there were dramatic changes in cardiac output. Our study of normal labour in women without epidural anaesthesia reported an increase in basal cardiac output (between contractions) of 12% that was mainly the result of an increase in stroke volume and occurred during the first stage of labour (fig 2). Cardiac output during contraction increased progressively as labour advanced till, at full dilatation of the cervix, cardiac output had increased by a mean value of 34%. Early on in the first stage of labour this increase in cardiac output during contractions seemed to be caused by an increase in stroke volume but later on heart rate also increased.

Haemodynamic changes during the puerperium

A dramatic increase in stroke volume was reported immediately after delivery, possibly caused by the relief of caval occlusion.[18] Cardiac output according to previous studies returned to non-pregnant values at six weeks.[8 13 18] In our studies both cardiac output and heart rate had returned to the pre-pregnant values by two weeks after delivery (fig 3). Stroke volume had also decreased by two weeks although there was a further small reduction up to six months after delivery. If this process was looked at even more closely it became obvious that for the first two days after delivery stroke volume remained at the high values seen during pregnancy and thereafter fell dramatically. Heart rate remained raised during the first 24 hours after delivery and fell away dramatically over the next 10 days. Cardiac output remained up for 24 hours and then fell progressively until the tenth day.

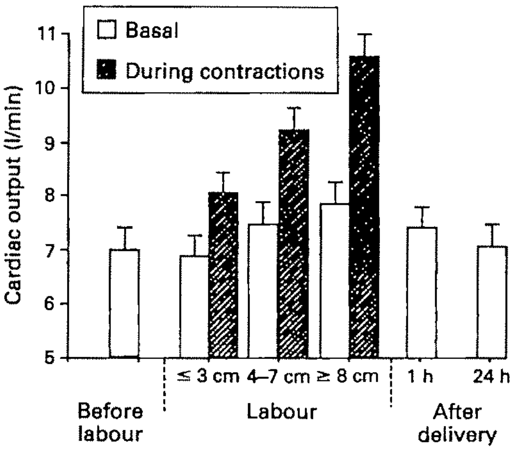

Figure 2 Changes in cardiac output and stroke volume during normal labour.

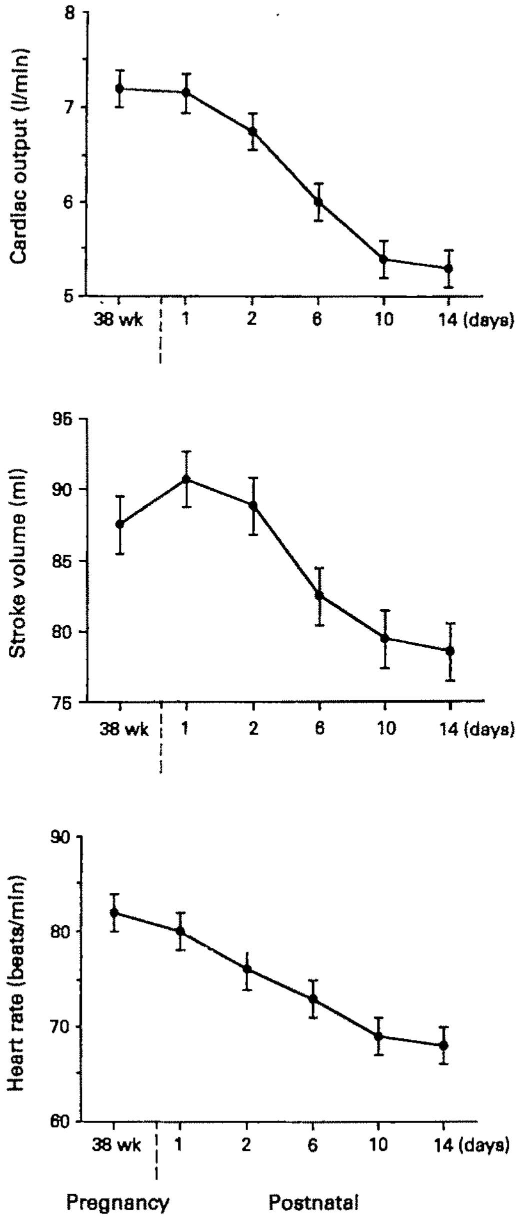

Figure 3 Changes in heart rate and cardiac output after normal delivery

Structural cardiac changes secondary to pregnancy

During our serial study the cross sectional areas of the aortic, pulmonary, and mitral valves were measured throughout pregnancy.[10] All three increased by between 12% and 14%, the changes being evident by 12 weeks' gestation and continuing throughout pregnancy.

Haites *et al* described the aortic minute distance (velocity integral × heart rate).[19] This index reflected changes in cardiac output in the non-pregnant state and had been suggested for use in pregnancy.[20] The increase in cross sectional area described above means that the use of stroke distance or minute distance as analogues of stroke volume or cardiac output in pregnancy will lead to an underestimate of the change shown by the full echo Doppler technique. Pregnancy produces an increase in left ventricular wall thickness and mass[8 21 22] that is demonstrable during the second trimester and most marked at the end of pregnancy. In contrast to the functional changes, structural adaptation takes much longer (up to 12 weeks) regress after delivery. The analogy with the exercise effect in the normal heart is interesting.

Factors influencing the changes in cardiac output and function during pregnancy.

Venous return is bound to be increased during pregnancy probably because of the 40% increase in blood volume.[23] Serial measurement of left atrial and left ventricular end diastolic dimensions by M mode support this.[8 14 24] The cavity dimension seemed to increase primarily during the second trimester at the time when plasma volume has been shown to rise. Despite this increase in volume the pressures within the lung vessels and the central venous pressures did not increase during pregnancy[16] possibly because of ventricular dilatation and reduction in vascular resistance in both the systemic and pulmonary beds.

There is little doubt that blood pressure falls serially during pregnancy reaching its lowest level at about 20 weeks' gestation.[24 25] From then until term there is a progressive increase in blood pressure both systolic and diastolic. Overall the fall in diastolic pressure is greater than the systolic change and the total systemic resistance falls considerably during pregnancy. In our own study systemic vascular resistance had fallen by 34% at 20 weeks' gestation.[24] Thereafter there was a small increase to term. Overall these results suggest that cardiac afterload is significantly reduced during pregnancy possibly associated with a fall in aortic compliance and in viscosity.

Myocardial contractility is the third component of cardiac function. It is extremely difficult to assess in vivo although several studies of M mode indices have shown that ejection fraction and mean rate of circumferential fibre shortening increase during pregnancy.[21 24 26] This increase occurs during the first two trimesters and seems to fall away during the third. The major problem lies in the interpretation of these findings because all these indices are affected by changes in heart rate, preload, and afterload. The only group to have studied intrinsic left ventricular contractility by the left ventricular work index is Clark *et al*.[16] In normal pregnant subjects they found a statistically insignificant increase at 36–38 weeks' gestation compared with postnatal control values.

Summary

The first haemodynamic change during pregnancy seems to be a rise in heart rate. Starting between two and five weeks this continues well into the third trimester. Stroke volume increases slightly later than the heart rate and continues throughout the second trimester after an augmentation of venous return and a fall of systemic vascular resistance and afterload. Myocardial contractility is probably slightly increased. During the third trimester there is relatively little change in these cardiac indices. After delivery there is a very early and dramatic reduction in volume loading followed by a return towards normal cardiac output. Structural changes within the heart reflect the volume loading of pregnancy and include dilatation of the valve ring and increase in myocardial thickness. Post partum resolution of the ventricular hypertrophy seems to take longer than the rest of the post partum changes. The resemblance to the cardiovascular changes associated with training and exercise are fascinating and worthy of further study.

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REVIEW

Non-rheumatic atrial fibrillation: warfarin or aspirin for all?

J Nolan, P Bloomfield

Stroke is the third most common cause of death in the United Kingdom after ischaemic heart disease and cancer. Disabled patients who survive an acute stroke place a great social and economic burden on the community—stroke prevention is therefore a priority. Cerebral infarction accounts for almost 80% of all first strokes. A significant proportion of these are embolic in origin and associated with atrial fibrillation. Anticoagulant and antiplatelet drugs may reduce the risk of stroke in such patients by preventing the formation of thrombus in the heart. What is the evidence that such treatment used as a primary preventive measure reduces the incidence of stroke in patients with atrial fibrillation? Which subgroups of patients are at high and low risk of stroke, who should be treated, and with what?

Conventional indications for anticoagulant treatment in atrial fibrillation

There is general agreement that patients with rheumatic or thyrotoxic atrial fibrillation and patients undergoing direct current cardioversion for fibrillation are at high risk of embolic stroke and that this risk is reduced by primary prevention with warfarin,[1-6] although no adequate prospective randomised clinical trials have examined this in detail. Patients with a recent ischaemic stroke and atrial fibrillation may benefit from anticoagulation as a secondary preventive measure[7 8]; this issue is currently being prospectively investigated in the European Atrial Fibrillation Trial which may provide a clear answer when it reports in the near future.

Non-rheumatic atrial fibrillation

Atrial fibrillation occurring in the absence of rheumatic heart disease (non-rheumatic atrial fibrillation) is a common condition with an overall prevalence of 0·4% in the adult population.[9] Its prevalence rises from 0·5% below the age of 60[10] to 10% over the age of 75.[11] Each year approximately 0·5% of people aged over 60 will develop non-rheumatic atrial fibrillation. In most cases non-rheumatic atrial fibrillation occurs in association with hypertension, ischaemic heart disease and congestive heart failure.[12 13]

Non-rheumatic atrial fibrillation is clearly associated with an increased risk of stroke. In both the Framingham Study[14] and a study of British civil servants[15] there was a fivefold increase in the risk of stroke in such patients. The annual risk of stroke in patients with non-rheumatic atrial fibrillation is approximately 5%.[12 16]

Subgroups of patients with non-rheumatic atrial fibrillation with different risk profiles for stroke can be identified. Chronic or paroxysmal atrial fibrillation occurring in patients below the age of 60 years in the absence of detectable cardiac disease (so called "lone atrial fibrillation") is associated with a low risk[17-20] with stroke rates of 1·3% over a 15 year period (identical to that of an age and sex matched population).[21] Paroxysmal atrial fibrillation may be associated with a lower risk of stroke than established atrial fibrillation,[13] though this has not been well substantiated. The risk of stroke is higher in older patients and those with a history of previous thromboembolism, atrial fibrillation of recent onset, or associated cardiovascular disorders such as heart failure, cardiomyopathy, ischaemic heart disease, or hypertension.[22-26] Patients with echocardiographic evidence of severe left ventricular dysfunction or left atrial enlargement are also at greater risk of stroke.[27]

Pathophysiology of stroke associated with atrial fibrillation

A large proportion of patients in recent studies of non-rheumatic atrial fibrillation had associated cardiac disorders (myocardial infarction, congestive heart failure, hypertension, mitral regurgitation, or calcification of the annulus of the mitral valve). Thrombus is known to develop in association with altered blood flow through the atria or in the left ventricle in such patients. Estimates from several clinical and necropsy series suggest that between 50% and 75% of ischaemic strokes in patients with non-rheumatic atrial fibrillation are due to emboli from the heart.[28 29] Most nonembolic strokes in such patients are caused by coexistent atherosclerotic cerebrovascular diseases. Fibrin formation may be more active than platelet activation in the production of potential emboli in areas of stasis within dilated cardiac chambers, and these emboli may therefore be preventable with warfarin but not

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aspirin. Activation of platelets may be the dominant mechanism for the formation of emboli in patients who have turbulent flow over atherosclerotic plaques or across cardiac lesions such as calcified or thickened mitral valves, and both warfarin and aspirin may therefore be effective in these patients.[30]

Anticoagulant treatment in non-rheumatic atrial fibrillation

The potential benefit of anticoagulant treatment as primary prevention to reduce the risk of stroke in patients with non-rheumatic atrial fibrillation has been studied in four randomised prospective trials published in the past three years.[31–34] All were terminated early on the recommendation of their data monitoring committees.

In the Copenhagen Atrial Fibrillation, Aspirin Anticoagulation (AFASAK) Study[33] 1007 patients with established atrial fibrillation were randomised to receive warfarin (dose adjusted to give an international normalised ratio (INR) of 2·8–4·2), low dose aspirin (75 mg daily), or placebo. The mean age of the patients was 74 years; 8% had a history of myocardial infarction and 50% a history of heart failure. The primary end point of the trial was the occurrence of a thromboembolic event (all strokes, transient cerebral ischaemia, or systemic embolism). Most (78%) of thromboembolic events that occurred were cerebral. Patients were followed up for at least two years and there was a significant 64% reduction in the annual thromboembolic event rate from 5·5% per annum in the aspirin and placebo group to 2·0% per annum in the warfarin treated group.

In the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF)[32] 420 patients with atrial fibrillation (approximately one third of whom had paroxysmal atrial fibrillation) were randomised to receive warfarin (INR 1·5–2·7) or to a control group receiving no anticoagulants. The control group could be prescribed antiplatelet agents and almost half of the patients received aspirin. The mean age of the patients was 68 years: 13% had a history of myocardial infarction and 25% a history of heart failure. The primary end point was ischaemic stroke. After an average follow up period of 2·2 years there was a significant 86% reduction in the annual stroke rate from 3% in the control group to 0·4% in the anticoagulated group.

In the Stroke Prevention in Atrial Fibrillation (SPAF) Study[31] 1330 patients (mean age 67 years) with atrial fibrillation (paroxysmal in one third of patients) were studied. Most patients (71%) were men; 13% had a history of myocardial infarction and 19% a history of heart failure. There were 627 patients who were considered suitable for anticoagulation and they were randomised to receive warfarin (INR 2·0–4·5), aspirin (325 mg daily), or placebo. There were 703 patients who were not considered suitable for anticoagulation and they were randomised to receive aspirin (325 mg daily) or placebo. The primary end point of the study was the occurrence of a thromboembolic event (ischaemic stroke or systemic embolism) and once again most (96%) of these events were cerebral. After a mean follow up period of 1·3 years there was a significant 67% reduction in the annual thromboembolic event rate in those receiving warfarin compared with those in the placebo group (2·3% *v* 7·4% per year).

The Canadian Atrial Fibrillation Anticoagulation Study[34] was similar in design to the BAATAF study. This study also showed a reduction in the incidence of stroke with warfarin treatment but the results did not reach statistical significance because after 378 patients had been randomised it was terminated when the positive findings in the above studies were reported.

Taken together, these large randomised prospective studies indicate that warfarin is effective in reducing the incidence of stroke and systemic embolism in patients with non-rheumatic atrial fibrillation.

The major danger of warfarin treatment is the risk of bleeding, which may counterbalance the beneficial effect of treatment. In both the SPAF and BAATAF studies the risk of major bleeding complications (requiring admission to hospital, blood transfusion, surgical intervention, or leading to death or permanent residual neurological deficit) was not increased by warfarin treatment. In the AFASAK study, however, with warfarin treatment the annual rate of major bleeding complications was 3·5% compared with 0·2% for aspirin and 0% for placebo. This difference may be due to several factors. Patients in the BAATAF study were treated with low intensity warfarin. Because lower levels of anticoagulation are associated with a lower risk of haemorrhagic complications[35] this may explain the lower rate of bleeding complications in this study. Only about 10% of the patients eligible for the SPAF study were randomised, and this selection process may have produced a study group at low risk of bleeding complications. In the AFASAK study 40% of eligible patients were randomised. The use of high intensity warfarin treatment in an unselected population may explain the increased rate of major bleeding complications in the AFASAK study compared with the SPAF and BAATAF study.

Bleeding complications and control of anticoagulation

The risks of bleeding complications reported in the studies of anticoagulation in non-rheumatic atrial fibrillation need to be compared with those reported from studies of anticoagulant use in other conditions. In a long-term evaluation of heart valve prostheses recently reported from our hospital[36] the actuarial risk of bleeding severe enough to cause admission to hospital or blood transfusion was 18·6% at 12 years, producing an annual bleeding rate of 1·7% that is similar to that reported in the SPAF and BAATAF trials. In a similar trial from the Veterans Administration in the United States[37] the risk of bleeding was almost three times greater—a finding almost certainly due (at least in part) to the difference between United States and United Kingdom practices for control of warfarin treatment.[38] It has recently been recognised that commercially available thromboplastins used in the United States are less sensitive than those in use in the United Kingdom. This has resulted in greater degrees of anticoagulation and larger doses of warfarin being used in the past in the United States to achieve similar prothrombin ratios to those used in monitoring anticoagulant treatment in Europe.[39] Recognition of this problem has led to the widespread use of the INR to control warfarin treatment in the United States. Because difficulties remain in the conversion factors used to translate locally derived prothrombin ratios the INR ranges of anticoagulation quoted in different studies may not be directly comparable.[40] These differences are, however, quite small and it seems evident from the BAATAF trial that the beneficial effects of warfarin in non-rheumatic atrial fibrillation can be realised at a lower level of anticoagulation with an INR of 1·5–2·7. Furthermore in two recently published randomised trials in patients with prosthetic heart valves[41 42] lower intensity treatment with warfarin was no less efficacious than higher intensity treatment and was associated with a lower incidence of bleeding problems. Warfarin is often held to be contraindicated in elderly patients. A recent overview of published clinical trials showed no relation between age and the risk of bleeding during warfarin treatment.[43] Carefully controlled low intensity warfarin is safe, even in the elderly, provided there are no obvious contraindications.

Is aspirin a viable alternative to warfarin?

Aspirin is a safe and convenient alternative to warfarin and would be preferable if it was effective in reducing stroke in non-rheumatic atrial fibrillation. A daily dose of 75 mg of aspirin had no beneficial effect in the AFASAK study. The BAATAF study was designed only to examine the efficacy of warfarin, and did not report on the effect of aspirin. In the SPAF study aspirin (325 mg daily) significantly reduced (42%) the thromboembolic event rate from 6·3% to 3·6% per year compared with placebo. The results of the direct comparison of warfarin and aspirin in this study were not reported because of the small numbers of patients enrolled: but this comparison is continuing as SPAF II.

Aspirin did not significantly increase the number of haemorrhagic episodes compared with placebo in both the AFASAK and the SPAF studies. Antiplatelet treatment with aspirin in the dose range 75–325 mg daily is clearly safer than warfarin anticoagulation. Aspirin may have been effective in the SPAF study and not the AFASAK study because of the higher dose used or because as previously noted the patients in the AFASAK study were older and had a higher incidence of associated cardiac disease.

Conclusion

Giving warfarin to 2–5% of the population over the age of 60 years and as many as 10% over the age of 75 to reduce the risk of stroke is a daunting prospect. The burden on general practice and anticoagulant clinics would be substantial. It is clear, however, that patients with sustained or paroxysmal non-rheumatic atrial fibrillation have an annual risk of stroke of about 5%, and that this risk can be reduced by anticoagulation with warfarin without an excessive risk of haemorrhagic complications. Recent estimates indicate that for every 1000 patients with non-rheumatic atrial fibrillation warfarin treatment for one year would prevent between 15 and 50 episodes of ischaemic stroke or systemic embolism at a cost of approximately 4–6 episodes of major bleeding.[44] The potential risks and benefits of treatment need to be carefully weighed for each individual patient. Patients at high risk of stroke (those aged over 60 years with a dilated left ventricle, a large left atrium, coexistent heart failure, or ischaemic heart disease) and low risk of a bleeding complication stand to gain most from warfarin treatment. We believe that such patients who have no contraindications, and in whom management of anticoagulation is feasible should receive warfarin. Because warfarin given at a lower intensity of anticoagulation is effective and is likely to be associated with a lower incidence of haemorrhagic complications, a low intensity regimen, aiming for an INR of 1·5–2·7, should be used.

Patients below the age of 60 with chronic or paroxysmal atrial fibrillation in the absence of any other cardiac disease are at low risk of embolisation. In this group the risks of warfarin treatment outweigh the benefits and such patients should not be anticoagulated.

For those patients with non-rheumatic atrial fibrillation at high risk in whom anticoagulation is contraindicated or cannot be reasonably managed, the SPAF II study suggests that aspirin (325 mg daily) is an alternative that may be effective in reducing the risk of cardiogenic embolism and stroke. Currently, aspirin cannot be recommended as an alternative to warfarin for the primary prevention of stroke in all patients with non-rheumatic atrial fibrillation, although the SPAF II study should clarify the relative merits of these two treatments.

All patients with non-rheumatic atrial fibrillation should now be carefully evaluated with a view to treatment with low intensity warfarin (or aspirin 325 mg daily if warfarin is contraindicated) because such treatment will reduce the high annual risk of a potentially devastating and irreversible embolic stroke.

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Neurological comment

The dilemma of whether anticoagulation treatment reduces the likelihood of ischaemic stroke (and embolism generally) in patients with non-rheumatic atrial fibrillation, without causing unacceptable risk has been around for decades. At long last there are enough good data for reviewers like Dr Nolan and Dr Bloomfield to write something other than an expression of opinion based on anecdote and non-randomised comparisons. The risks of anticoagulants have been well enough appreciated but now the recent randomised trials give us some idea of the benefit of treatment, though an even better idea would come from a formal overview (or meta-analysis) of all the available randomised trials, particularly if the trialists were to pool individual patient data to examine risk and benefit in subgroups of interest (for example, the elderly and those with chronic fibrillation rather than paroxysmal fibrillation). Of course the costs must be considered as well. I suspect that providers and purchasers in the reformed NHS have very little idea of what anticoagulation really costs (what price a gastrointestinal haemorrhage?) and no idea at all about the cost of a stroke (what price granny's stroke if she can no longer look after the grandchildren to allow their mother to go out to work?). If treating 1000 fibrillating patients for a year does prevent about 25 of them from having a stroke,[1] then 40 people must be treated to prevent one having a stroke during that period. "Is this worthwhile?" and "can we afford it?" are questions that providers and purchasers had better start working on fast, because I am certain that cardiologists and others will be anticoagulating a lot more patients, as Nolan and Bloomfield recommend. If aspirin is as effective or nearly as effective as anticoagulation then this treatment seems to be less risky and also more cost effective. This question re-emphasises just how extraordinarily important it is that recruitment into SPAF II and similar trials continues and that it is not assumed that for primary prevention of stroke in non-rheumatic atrial fibrillation it must be anticoagulation or nothing.

These, however, are not issues that neurologists are supposed to debate—because we see patients after the stroke. Of course, we certainly will debate them vigorously if anyone suggests that our clinics are turned over to anticoagulating thousands of fibrillating prestroke patients rather than allowing us to get on with neurology—which is not quite so therapeutically hopeless as some cardiologists seem to think. The main questions for neurologists and others who treat stroke patients are:

(*a*) In a fibrillating stroke patient was the stroke caused by cerebral infarction or primary intracerebral haemorrhage (PICH), a distinction that can only be made reliably in life with an early computed tomogram (CT) scan. Scanning patients more than a week or two after onset does not exclude PICH because the high intensity signal of the haematoma may have gone by then.[2] One cannot assume that the stroke must have been caused by an infarct (about 11% of patients with a first stroke caused by primary intracerebral haemorrhage are in atrial fibrillation[3]).

(*b*) If the stroke was caused by an infarct, was this related to the atrial fibrillation or was it due to something else requiring quite different treatment (for example, carotid stenosis and embolism to the brain, vasculitis, or trauma to neck arteries?) Usually the diagnosis of cardioembolic stroke is one of exclusion of other more likely causes. Even echocardiography is no great help because seeing thrombus in the left atrium does not necessarily mean that a bit of thrombus has embolised or that another bit will embolise, and if there is no left atrial thrombus this may be because it is too small to be seen or because it has all embolised.

(*c*) If the patient has, we assume, embolised from the left atrium to the brain and was already taking anticoagulants we must consider whether the dose was adquate. If the patient was not being treated with anticoagulants, should this treatment be started for secondary prevention of stroke? This is difficult to answer because the risk-benefit relation (and cost) may be quite different from primary prevention. However, the European Atrial Fibrillation trial has now finished recruitment and an answer to the question may emerge after a few years of follow up. In the meantime, it seems reasonable to use aspirin for secondary prevention, because it is at least safe and reduces the risk of serious vascular events by about 25% in a broad range of "at risk" patients presenting with vascular disease, including ischaemic stroke.[4]

(*d*) If the stroke was haemorrhagic and the patient was on anticoagulants should the treatment be stopped, and if so for how long? This is a very tricky question. Firstly, we must be quite sure that the haemorrhage was a primary event rather than haemorrhagic transformation of an infarct, a distinction that in some cases can be surprisingly difficult on computed tomography. The definitive test is to have an early computed tomogram showing an infarct which on a later CT scan shows haemorrhagic transformation. Haemorrhagic transformation can occasionally occur remarkably early after stroke onset, perhaps within hours.[5] This then is another reason to get a CT scan at once in a fibrillating stroke patient. If there is a primary intracerebral haemorrhage then I think anticoagulants should be stopped and the reason for using them at all in that patient reviewed. If there was, and still is, a really good indication for anticoagulation, and if the PICH was thought to be due to excessive anticoagulation, and if such an excess can be avoided in the future, then maybe cautious anticoagulation should be restarted after two or three weeks.

The recent randomised controlled trials of anticoagulation have been landmarks but like all good experiments they have raised more questions. The dilemmas are still there but they are different dilemmas, not so much to do with the effectiveness of anticoagulation for primary stroke prevention but with cost effectiveness: is aspirin just as good and much cheaper and how should fibrillating patients be managed *after* the stroke when primary prevention has failed?

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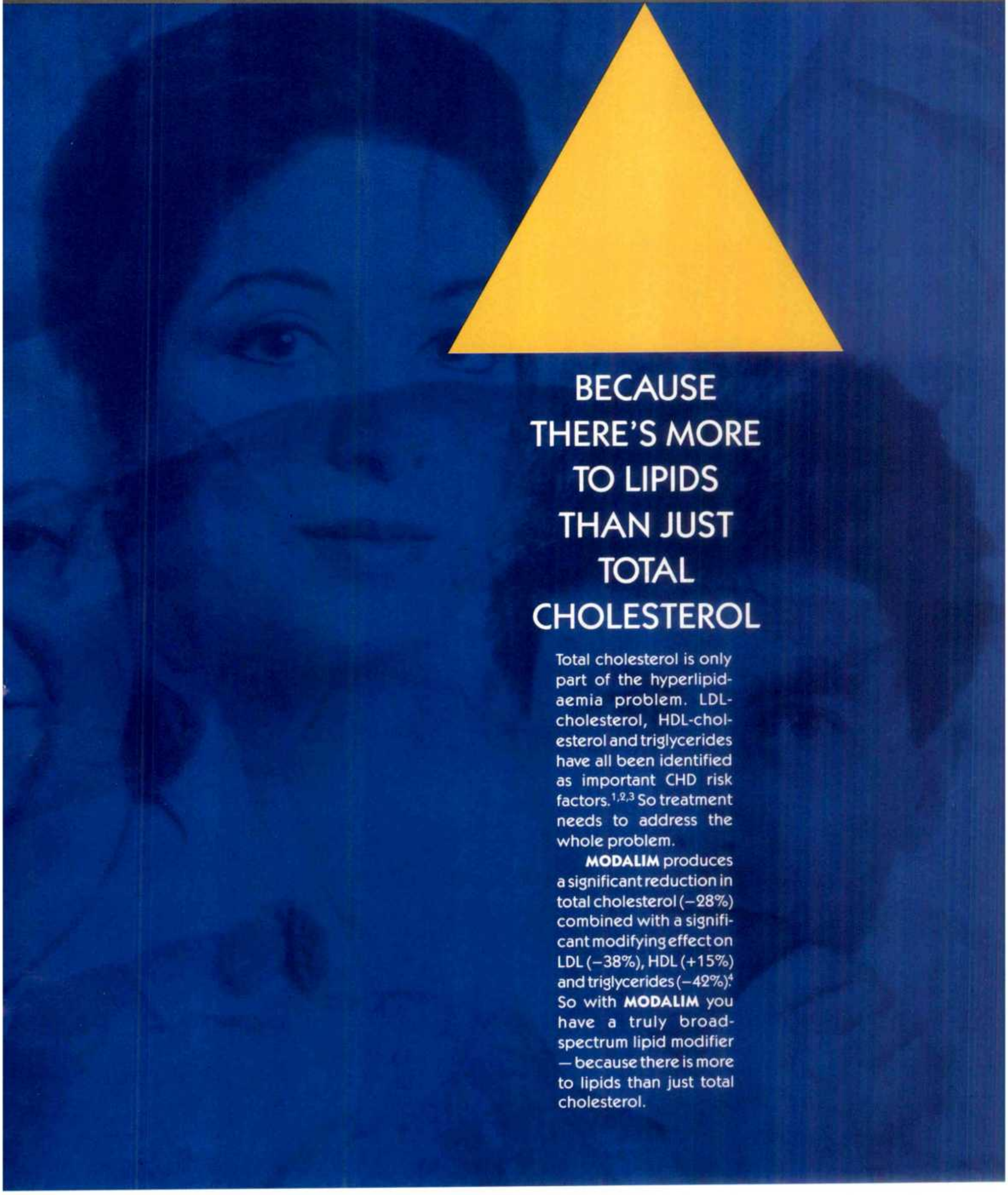

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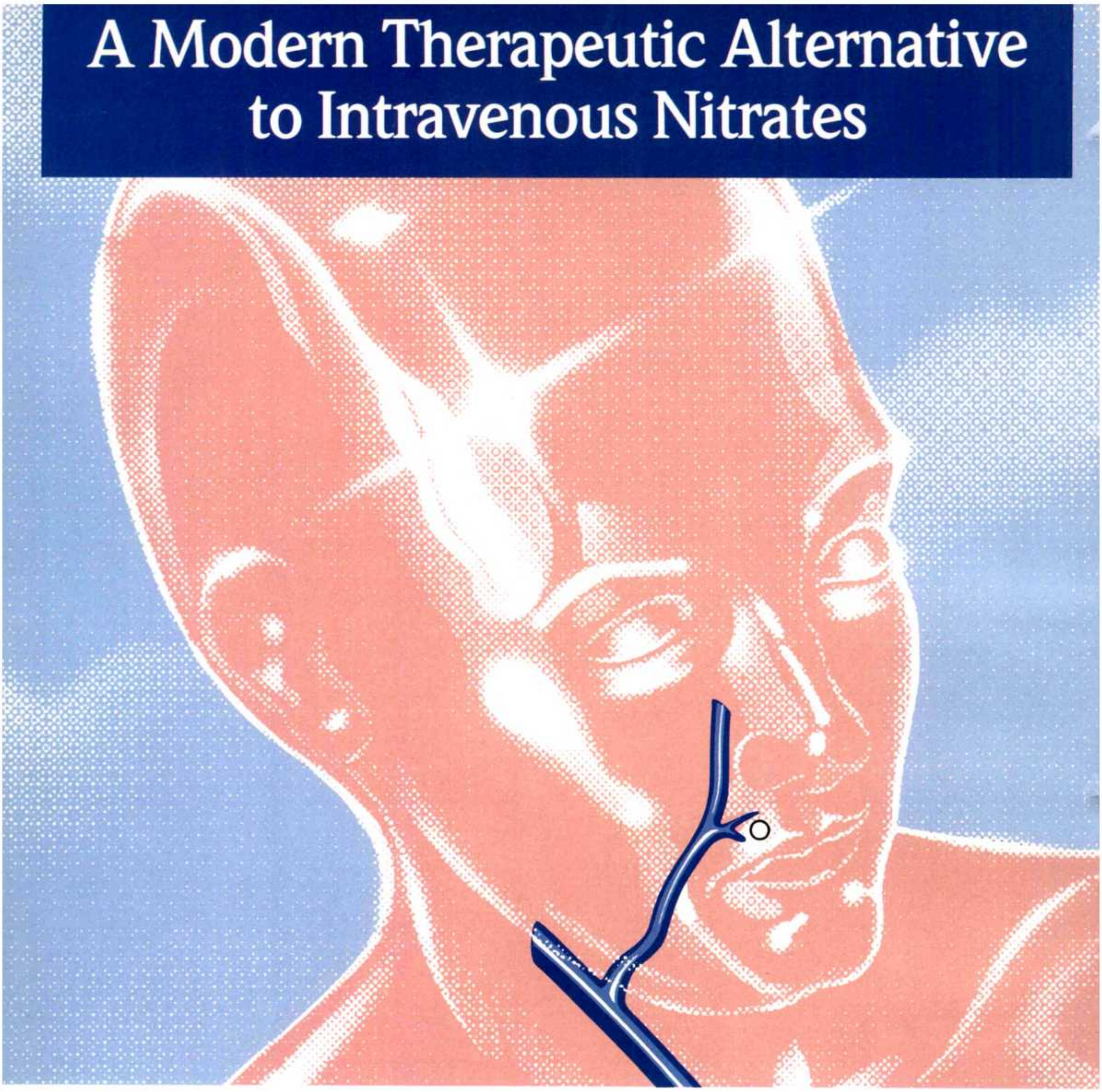
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Myocardial dysfunction in patients infected with HIV: prevalence and risk factors

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Abstract

***Objectives*—To determine the prevalence of and risk factors for myocardial dysfunction in HIV infection.**

***Subjects*—173 patients infected with HIV underwent echocardiography. 119 were current or previous injection drug users, 38 were homosexuals, 10 were haemophiliac patients, and six were heterosexual.**

***Main outcome measure*—Detection of impaired ventricular function.**

***Results*—26 patients with abnormalities of ventricular size or function or both were identified. The abnormality was (*a*) dilated cardiomyopathy in 13 patients (eight homosexuals, three drug users, and two haemophiliacs) with a mean CD4 count of 38 cells/mm^3, which accords with end-stage disease (in addition, three patients were identified as having borderline impairment of left ventricular function); (*b*) left ventricular dilatation without loss of function in a further six patients; and (*c*) isolated right ventricular dilation in seven patients. Follow up echocardiograms were obtained in 71 patients, 18 of whom had myocardial dysfunction (103 echocardiograms, mean (SD) 2·5 (0·6) scans per patient, mean interval 200 (116) days, range 14–538 days). These showed that in four cases of isolated right ventricular dilatation, one of isolated left ventricular dilatation, and two with borderline left ventricular dysfunction myocardial function subsequently reverted to normal. There was no excess of exposure to zidovudine in the patients with myocardial dysfunction. Similarly, patients with myocardial dysfunction had no serological evidence of excess secondary infection with *Toxoplasma gondii* and cytomegalovirus.**

***Conclusions*—There was a high prevalence and wide range of myocardial dysfunction in HIV positive patients. Dilated cardiomyopathy was a feature of advanced HIV disease and affected all major risk groups for HIV infection. In contrast, isolated dilatation of either ventricle occurred at an earlier stage of HIV infection and, particularly in the case of the right ventricle, often was transient. Neither treatment with zidovudine nor infection with *Toxoplasma gondii* or cytomegalovirus seemed to be responsible for these findings.**

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The effects of the human immunodeficiency virus (HIV) are protean and all major organs are potential targets for infection. Cardiac involvement in HIV disease includes pericardial effusion (a common index condition in Africa), infiltration by lymphoma and Kaposi's sarcoma, and infective endocarditis, which is usually associated with injection drug use.[1] Isolated case reports and small series dominated by one or other risk group have shown that HIV is also associated with heart failure secondary to myocarditis and dilated cardiomyopathy.[2-5] These two conditions may represent a continuum with myocarditis progressing to cardiomyopathy in some patients. There are many potential causes of myocarditis in HIV disease including HIV itself[6] and infection with other organisms such as *Toxoplasma gondii* and cytomegalovirus.[1] Myocardial dysfunction in HIV infection could also be an effect of zidovudine, a drug now commonly prescribed for HIV positive patients, which causes myopathy of skeletal muscle secondary to impaired replication of mitochondrial DNA.[7]

To date there has been no definitive assessment of the natural history and associations of cardiac dysfunction in the entire range of adult groups infected with HIV. We therefore examined 173 patients drawn from all the major risk groups for HIV infection in a prospective echocardiographic study whose principal aims were to establish the prevalence of myocardial dysfunction and determine its association with variables such as the extent of HIV disease, opportunistic infection, and adjuvant therapy.

Patients and methods

Over an 18 month period, 173 HIV positive patients drawn from all the current major United Kingdom risk groups for HIV infection—38 homosexuals, 119 injection drug users, 10 haemophiliacs, and six heterosexuals—were examined echocardiographically on one or more occasions. Hewlett Packard Sonos 100 and 1000 machines with 2·5 and 3·5 MHz transducers were used to measure left ventricular end diastolic and end systolic size. On-screen callipers were used to make these measurements from M mode tracings derived from a short axis view at the level of the papillary muscles of the mitral valve with the patients in the left lateral position. Fractional shortening was calculated as the difference between the two diameters divided by the end diastolic value. All the echocardiographic data were stored on videotape for subsequent detailed analysis by three independent observers including the operator. Whereas the operator was necessarily aware of the clinical history of the patients, the other two observers reported the echocardiograms independently of the operator, and were unaware both of the clinical history and the previous ultrasound result.

DEFINITIONS

Dilated cardiomyopathy—A fractional shortening of <28% and global left ventricular hypokinesia reported by all three independent observers.

Borderline left ventricular dysfunction—A fractional shortening of <28% and global left ventricular hypokinesia reported by only two of the three independent observers.

Isolated left ventricular dilatation—Left ventricular end diastolic diameter >58 mm with a fractional shortening >28%.

Isolated right ventricular dilatation—Right ventricle equal in size or larger than the left ventricle on cross sectional views.

In 22 patients precise M mode measurements could not be obtained and assessment was made exclusively on the cross sectional views. Three of these patients were classified as having cardiac dysfunction (two dilated cardiomyopathy, one isolated right ventricular dilation) and 19 were thought to be normal.

We calculated the total exposure to zidovudine in each patient by multiplying the daily dose by the number of days for which that dose had been prescribed. Blood was obtained at the time of the ultrasound study in approximately 80% of patients. Because CD4 counts were checked regularly in most patients, it was possible to obtain blood within one month of the ultrasound study in the remaining patients. Similarly, stored serum from blood taken at or shortly after the ultrasound examination was analysed for evidence of infection with *Toxoplasma gondii* and cytomegalovirus. A toxoplasma dye test was performed if the preliminary *Toxoplasma gondii* screen was positive. When this was greater than 250 IU/ml, IgM was measured to establish whether the infection was recent. A cytomegalovirus titre of between 1 in 4 and 1 in 32 inclusive was interpreted as evidence of past infection. In patients with titres of more than 1 in 32, IgM was measured to determine whether the infection was primary or recurrent. We planned to undertake repeat echocardiograms in all patients every six months, or sooner where clinically indicated. More frequent studies would have been impossible in a population consisting mainly of injection drug users who often had to be coaxed into the ultrasound suite and to remain still for the examination. Furthermore, there were potential ethical objections to performing large numbers of studies on patients whom many felt were being over investigated already. In the event, of the 173 patients recruited, 71 underwent further echocardiography. Thirty six patients died before their repeat study, 53 did not return for follow up or attended clinics outside Edinburgh, and 13 had their first echocardiogram less than six months before the end of the study period.

Results in the text are given as the mean (SD). χ^2 and Mann-Whitney U tests were used to compare different subgroups of patients.

Results

Table 1 shows the clinical and haematological characteristics of all 173 patients. The mean CD4 count of the homosexuals, which was significantly less than that of all the other risk groups, indicated more advanced disease. This is compatible with homosexuals being the first group to acquire HIV infection in the early 1980's.

Twenty nine patients (nine homosexuals, 18 drug users, and two haemophiliacs) had evidence of myocardial dysfunction on their first ultrasound study (table 2). The remaining 144 patients had structurally normal hearts.

ECHOCARDIOGRAPHIC ABNORMALITIES OF VENTRICULAR SIZE AND FUNCTION (TABLE 2)

Dilated cardiomyopathy was found in 13 patients (eight homosexuals, three drug users, and two with haemophilia) all of whom had advanced HIV disease (CD4 count 38 (55) cells/mm^3) (table 2). Mean fractional shortening for this group was 20·9 (4·7)% (range 14–27%). There was a significant excess of homosexuals in this group (21·1% affected *v* 2·5% of injection drug users affected, $p < 0·001$), probably because the homosexual patients had more advanced HIV disease than the drug users. At least seven of these patients had symptoms and signs of heart failure including fatigue, breathlessness, tachycardia, ankle oedema, gallop rhythm, and pulmonary crackles. Before echocardiographic examination only three patients were thought to have a cardiac disorder. Five patients had repeat echocardiography (2·2 (0·5) echocardiograms per patient, mean interval 184 (154) days, range 49–476 days) and in every case there was evidence of persistent global impairment of left ventricular function (fig 1).

Borderline left ventricular dysfunction—There were three patients in this group. Their fractional shortening was 26 (1·7)% (range 24–27%). All three had symptoms of but no signs consistent with impaired left ventricular function. Two patients underwent repeat echocardiography, one five months later and the other on two occasions five and six months later. In both patients ventricular function had reverted to normal (fig 1). One of these patients was subsequently shown to have had *Pneumocystis carinii* pneumonia at the time of his initial echocardiogram.

Isolated left ventricular dilatation—Six patients had left ventricular dilation without loss of function. Their left ventricular end diastolic diameter was 60·7 (1·0) mm (range 59–62 mm) and their fractional shortening was normal at 36·5 (3·8)% (range 31–41%). There was no significant difference in fractional shortening compared with patients with normal hearts. Repeat echocardiography was performed in four of the six patients in this group (2·3 (0·5) echocardiograms per patient, mean interval 263 (149) days, range 171–523 days).

Table 1 Clinical profile of 173 patients with HIV infection

Risk group	*M*	*F*	*Age (mean (SD)) (range) (yr)*	*CD4* (mean (SD)) (range (cells/mm³)*
Injection drug users (n = 119)	79	40	29·6 (4·8) (22–44)	178 (189)† (0–931)
Homosexual (n = 38)	38	—	35·9 (7·9) (26–59)	72 (104)† (0–388)
Haemophiliac (n = 10)	10	—	37·9 (9·0) (28–56)	108 (121) (10–390)
Heterosexual (n = 6)	3	3	43·8 (15·0) (29–63)	128 (100) (3–243)

*Normal range for CD4 is 500–1500 cells/mm³.
†p < 0·0001.

In one patient ventricular function reverted to normal and three had persistent isolated left ventricular dilatation (fig 1). In this subgroup, there were no significant changes either in left ventricular end diastolic diameter (60·7 (0·6) mm to 60·3 (1·2) mm or in fractional shortening (34·0 (6·6)% to 36·7 (3·2)%).

Isolated right ventricular dilatation—Seven patients were found to have right ventricular dilatation with normal left ventricular size and function. Their fractional shortening was normal at 37·2 (7·7)% (range 28–51%). One patient had a large pericardial effusion and clinical and Doppler evidence of pulmonary hypertension. A subsequent perfusion lung scan indicated a high probability of multiple pulmonary emboli and treatment with warfarin was started. All seven underwent repeat echocardiography (2·6 (0·5) echocardiograms per patient, mean interval 240 (100) days, range 104–400 days). In four of these patients ventricular function subsequently became normal and three of them had had a chest infection at the time of their initial assessment (fig 1). Of the remaining three patients with persistent right ventricular dilatation one had pulmonary hypertension and another tricuspid incompetence due to previous endocarditis.

ADDITIONAL OBSERVATIONS

Fifty three patients with normal hearts subsequently had repeat echocardiography (78 echocardiograms, 2·5 (0·6) scans per patient, mean interval 193 (115) days) and in two dilated cardiomyopathy had developed (fig 1). Both these patients had late stage HIV disease and there was no evidence of recent acute secondary infection to account for the considerable decline in left ventricular function. Pericardial effusions were rare, being found in just four patients (one had isolated right ventricular dilatation and multiple pulmonary emboli, two had dilated cardiomyopathy, and the fourth had normal ventricles). Just one patient had active infective endocarditis affecting the tricuspid valve.

TREATMENT WITH ZIDOVUDINE (TABLE 2)

Dilated cardiomyopathy—All but one of these patients had been treated with zidovudine. However, neither the proportion of patients treated nor their mean total dose was significantly different from those patients without myocardial dysfunction.

Borderline left ventricular dysfunction—All three patients had received zidovudine but their mean total dose was not significantly different from those patients with structurally normal hearts.

Isolated left ventricular dilatation—Four of the six patients had undergone treatment with zidovudine, but again exposure was not significantly different from that in any other group.

Isolated right ventricular dilatation—Though the proportion of patients treated with zidovudine (6/7) was similar to all the other groups, the mean total dose (546·7 (246·3) g was significantly greater than that received by patients with dilated cardiomyopathy ($p < 0·05$) and those with structurally normal hearts ($p < 0·005$).

SECONDARY INFECTION WITH TOXOPLASMA GONDII AND CYTOMEGALOVIRUS

Of the 29 patients with cardiac abnormalities, 25 had never been infected with *Toxoplasma gondii*, two had evidence of past infection, and the status of two was unknown. Similarly, seven of these patients had never been infected with cytomegalovirus, three had experienced recurrent infection around the time of their echocardiogram, 16 had had an infection in the past, and the status of three was unknown. Infection with *Toxoplasma gondii* or cytomegalovirus was not significantly more common in patients with myocardial dysfunction than in patients with normal hearts (fig 2).

Serum was available from 11 of the 13 patients with dilated cardiomyopathy. Nine showed no evidence of exposure to *Toxoplasma gondii* and two had been infected in the past. Similarly, three patients had never been infected with cytomegalovirus and eight had evidence of past infection. Again, it was apparent that there was no excess secondary infection by these organisms in this group of patients.

Discussion

We have established that myocardial dysfunction in HIV positive subjects is common and affects all the major risk groups for HIV infection in the United Kingdom. In this series, dilated cardiomyopathy occurred late in the course of the disease whereas isolated left and right ventricular dilatation were found, sometimes transiently, at an earlier stage of

Table 2 Characteristics of patients with heart muscle disease and those without

	Homosexual (38)	*Drug users (119)*	*Haemophiliac (10)*	*Heterosexual (6)*	*CD4 (mean (SD) cells/mm³) (range)*	*Treatment with zidovudine*	
						Number (%)	*Total dose (mean (SD) g) (range)*
Cardiomyopathy (n = 13)	8	3	2	0	38 (55)* (0–145)	12 (92)	285·4 (245·8) (23·1–880·9)
Borderline (n = 3)	1	2	0	0	81 (64) (13–139)	3 (100)	525·9 (392·2) (215–966·6)
LV dilatation (n = 6)	0	6	0	0	215 (299) (4–783)	4 (67)	472·2 (234·0) (136–626)
RV dilatation (n = 7)	0	7	0	0	105 (105) (4–266)	6 (86)	546·7 (246·3)** (220·2–824 2)
Normal (n = 144)	29	101	8	6	160 (175) (0–931)	109 (76)	236·3 (334·3) (0·3–2500)

*p < 0·02 *v* normal; **p < 0·005 *v* normal and p < 0·05 *v* cardiomyopathy.

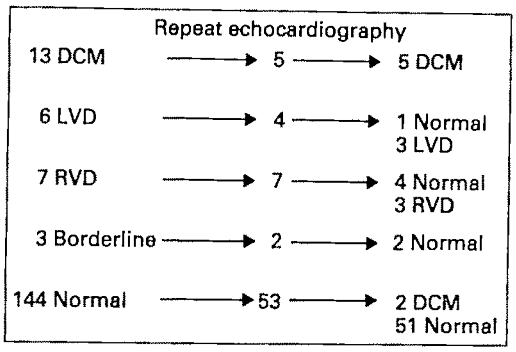

Figure 1 HIV heart muscle disease at follow up echocardiographic examination. DCM, dilated cardiomyopathy; LVD, isolated left ventricular dilatation; RVD, isolated right ventricular dilatation; borderline, borderline left ventricular dysfunction. Intervals (mean (SD)) between echocardiograms for each group are as follows: DCM = 184 (154) days; LVD = 263 (149) days; RVD = 240 (100) days; borderline = 153 (13) days; normal = 193 (115) days.

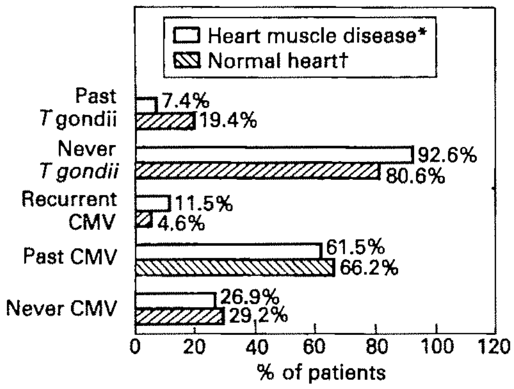

Figure 2 Information on infection with Toxoplasma gondii and cytomegalovirus in patients with HIV heart muscle disease and in patients with normal hearts. These results were derived from serological techniques.
** In two patients T gondii status was unknown and in three patients CMV status was unknown.*
† In 46 T gondii status was unknown and in 79 CMV status was unknown.

HIV infection and exclusively in injection drug users.

Deaths caused by opportunistic infection in HIV patients are declining and the median survival time from the diagnosis of AIDS is increasing.[8] This suggests that more patients will survive to develop the complications of late stage HIV disease including dilated cardiomyopathy.

Only some of the patients with dilated cardiomyopathy in our series had symptoms and signs consistent with impaired left ventricular function. In addition, before echocardiography less than 25% of this group was thought to have a cardiac disorder. Similar findings have been reported in an American series in which myocardial dysfunction was assessed in a small group of HIV positive children and these findings reflect the tendency to ascribe symptoms and signs of heart failure to non-cardiac causes.[9]

The cause of dilated cardiomyopathy in HIV infection is unknown. It may occur as a result of HIV itself acting either directly[6] or indirectly via immunological mechanisms.[10] Secondary infection with opportunistic organisms may also be important, particularly *Toxoplasma gondii* and cytomegalovirus which occur commonly in HIV infection and have been associated with myocarditis.[11 12] Drugs used in the treatment of HIV disease and its complications can have adverse cardiac effects. Zidovudine can cause a skeletal myopathy secondary to inhibition of mitochondrial DNA polymerase[7] and both pentamidine and ganciclovir can predispose patients to ventricular tachycardia.[13 14] Malnutrition has been reported in patients with HIV infection.[15] Selenium deficiency is thought to be responsible for a naturally occurring form of dilated cardiomyopathy in China (Keshan disease),[16] and it has also been associated with cardiac dysfunction in HIV infection.[17] Finally, cytokines such as tumour necrosis factor, have been found in high concentrations in HIV patients and these intercellular messengers may be responsible for some of the end-organ damage caused by the virus.[18] The aetiology of myocardial dysfunction in HIV infection is probably complex and multifactorial.

In our study we found no serological evidence either of recent infection with *Toxoplasma gondii* and cytomegalovirus or an excess of past infection with these organisms in the patients with myocardial dysfunction. Furthermore, separate analysis of the patients with dilated cardiomyopathy showed that some had never been infected by either organism. This militates against a potential pathogenetic role for these agents. However, it is possible that the results of serological tests are misleading in the context of the immune paresis associated with advanced HIV disease. Further work with the polymerase chain reaction, in-situ hybridisation, and immunohistochemical and culture techniques on endomyocardial biopsy and post-mortem material is required.

This is the first major study to show that treatment with zidovudine does not predispose towards cardiac dysfunction. Although most patients with myocardial dysfunction had been treated with zidovudine, neither the proportion of patients treated nor the mean total dose in each group was significantly different from the results in patients with structurally normal hearts. It is not clear why the group with isolated right ventricular dilatation had received a greater mean total dose of zidovudine than those with dilated cardiomyopathy and those with normal hearts. One possible explanation is that patients who have been in hospital with respiratory infections, and who were therefore more at risk of isolated right ventricular dilatation developing (see below), are also more likely to be treated with zidovudine than those remaining well in the community. However, in all the heart muscle disease groups some patients (except those described as having "borderline left ventricular dysfunction") had never received zidovudine. Moreover, in several patients with isolated right ventricular dilatation ventricular function subsequently reverted to normal while the patient continued to be treated with this drug. Taken together, these findings provide strong circumstantial evidence that zidovudine is not implicated in the development of myocardial dysfunction in HIV infection. It was not possible to determine whether all patients were taking their zidovudine as prescribed.

However, mean corpuscular volume was increased (a feature commonly associated with zidovudine treatment[19]) in most (100/118 (84·7%)) in patients who were prescribed zidovudine and, in addition, recognised side effects occurred in some patients. On balance, it is unlikely that compliance was different either in the various heart muscle disease groups or in those without cardiac dysfunction.

This study confirms the findings of Blanchard *et al* who showed that left ventricular function can be transiently impaired, and that the presence of left ventricular dysfunction on a single echocardiogram (the borderline group in our study) does not necessarily imply a poor prognosis.[20]

The significance of isolated left ventricular dilatation is unclear but it may represent an early stage in the development of dilated cardiomyopathy, despite the fact that in our series further echocardiograms did not show any significant change in left ventricular size or deterioration of function. The aetiology of isolated right ventricular dilatation is likely to be multifactorial. It may arise as part of a generalised myopathic process, from pulmonary hypertension due to pulmonary emboli or recurrent chest infections,[1 21] from volume overload secondary to tricuspid incompetence mediated by endocarditic valve damage, or from acute respiratory infection. In our series two of the three patients with persistent isolated right ventricular dilatation had either clinical evidence of pulmonary hypertension or a history of prior infective endocarditis of the tricuspid valve with Doppler evidence of significant tricuspid incompetence. Furthermore, three of the four patients with isolated right ventricular dilatation in whom ventricular function subsequently reverted to normal had a chest infection at the time of their initial ultrasound assessment. These findings suggest that many cases of isolated right ventricular dilatation are related to pressure/volume overload of the right ventricle or acute respiratory tract infection rather than a myopathic process.

In conclusion, myocardial dysfunction in HIV infection is common, takes various forms, and affects all major risk groups. Dilated cardiomyopathy occurs late in the course of HIV infection and is often associated with symptoms and signs that may be attributed mistakenly to other disease processes. Transient impairment of left ventricular function can also occur, possibly in relation to intercurrent infection. Similarly, isolated right ventricular dilatation is often associated with acute respiratory infection and therefore can also be transient. Persistence of dilatation may be related to pressure or volume overload of the right ventricle. Cardiac dysfunction does not seem to be related to treatment with zidovudine or infection with *Toxoplasma gondii* and cytomegalovirus. A direct effect of the virus itself remains a strong possibility. This possibility requires further research.

It is likely that better treatment of opportunistic infections and of HIV disease will result in more patients surviving to develop malignancies and end-organ failure.[8 22] We believe that heart failure due to myocardial dysfunction will become an important cause of morbidity and mortality in this group. Prompt recognition and treatment is important because palliative therapy with diuretics and vasodilators can be worthwhile.

We thank Dr J Inglis and Dr H Cubie of the Regional Virus Laboratory for performing the serological analyses, Mrs Marjorie Boubert for help with the echocardiography and Mrs Jean Cunningham for expert secretarial assistance.

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Similar prevalence of enteroviral genome within the myocardium from patients with idiopathic dilated cardiomyopathy and controls by the polymerase chain reaction

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Abstract

Objective—**To assess the prevalence and significance of enteroviral genome within myocardial biopsy specimens taken from patients with idiopathic dilated cardiomyopathy and from controls.**

Design—**Prospective evaluation of myocardial tissue for the presence of an enteroviral genome by the polymerase chain reaction.**

Setting—**A tertiary referral centre for patients with idiopathic dilated cardiomyopathy.**

Patients—**Tissue for the study came from 50 consecutive patients with dilated cardiomyopathy, 41 with other forms of heart disease and 34 from coroners' necropsy cases.**

Results—**Enteroviral genome was detected in 6/50 (12%) patients with dilated cardiomyopathy and 13/75 (17%) of the controls (not significant). No differences were seen between dilated cardiomyopathy patients with or without myocardial enteroviral genome in respect of age; duration of symptoms; proportion of patients with a premorbid acute viral illness, excess alcohol consumption, or hypertension; New York Heart Association functional class; measures of left ventricular function; or endomyocardial histology. Within the control group enteroviral genome was detected in 3/15 (20%) patients with ischaemic heart disease, 2/19 (10·5%) with valvar heart disease, 1/5 (20%) with specific heart muscle disease, 0/2 (0%) with congenital heart disease, and 7/34 (20·6%) cases of sudden death. During 2–52 month follow up (mean 22) 15/44 (34%) patients without myocardial enteroviral genome and 2/6 (33%) with myocardial enteroviral genome died suddenly or required orthotopic heart transplantation for progressive heart failure.**

Conclusions—**These findings do not support the hypothesis that persistent enteroviral infection is of pathogenic or prognostic importance in dilated cardiomyopathy but they are consistent with enterovirus being a common environmental pathogen.**

(*Br Heart J* 1992;68:554–9)

Enteroviruses, particularly coxsackie B viruses, are thought to be important in the pathogenesis of myocarditis and idiopathic dilated cardiomyopathy.[1,2] Although there is considerable support for an aetiological role of coxsackie virus in murine myocarditis and dilated cardiomyopathy[3,4] direct evidence in man is lacking.[5-7] The principal supporting evidence linking enteroviral infection to dilated cardiomyopathy is derived from several retrospective serological studies.[2,8,9] Enteroviruses, however, are endemic pathogens and enteroviral serology is highly complex; despite the introduction of specific assays for enteroviral immunoglobulin M[10] the significance of positive enteroviral serology remains unclear.[11] Recombinant deoxyribonucleic acid technology has been used to detect viral genome within myocardial biopsy material from patients with dilated cardiomyopathy and myocarditis. Initial studies of slot blot hybridisation[12,13] suggested that enteroviral genome was present in more than 50% of patients with established cardiomyopathy. Other groups, with different hybridisation techniques, have failed to confirm such a high prevalence of enteroviral genomic material in biopsy specimens from patients with myocarditis or dilated cardiomyopathy,[14-16] and accumulated data suggest a prevalence of 10%–20%. The discrepancies in the results of these studies may reflect differences in clinical diagnosis and the variable sensitivity and specificity of hybridisation assays used.

Gene amplification by the polymerase chain reaction (PCR) is a rapid and extremely sensitive technique.[17,18] Jin *et al*, using an enteroviral specific polymerase chain reaction in combination with slot blot hybridisation, reported a low prevalence (10%) of enteroviral genome within the myocardium of patients with dilated cardiomyopathy and myocarditis.[16] Unfortunately the low number of controls in this study makes interpretation of these results extremely difficult. In our study, we report the application of an enterovirus specific

PCR gene amplification technique to myocardial biopsy specimens taken from 50 patients with clinical dilated cardiomyopathy and from 75 biopsy specimens taken from patients with other forms of cardiac disease or cases of sudden death in the community.

Patients and methods

PATIENTS

Dilated cardiomyopathy

A clinical diagnosis of dilated cardiomyopathy was made according to World Health Organisation (WHO) criteria[19] in 50 patients (38 men, 12 women) whose ages ranged from 17–60 (mean (SD), 40 (12)) years. Fifteen patients had a history of chronic excess alcohol consumption (men > 8 units a day and women > 6 units a day for the preceeding five years) and nine patients had a historyof hypertension and were included in the study. All patients had an enlarged left ventricle on echocardiography (mean left ventricular end diastolic size 68 (8) mm) when expressed as a percentage of the calculated normal size by the method of Henry *et al* (mean 143% (19)% (normal range < 112%)).[20] All patients had impaired left ventricular systolic function as assessed by echocardiography (fractional shortening 13% (7)%), angiography (ejection fraction 28% (8)% and radionuclear ventriculography (ejection fration 23% (8)%. Functional classification with the new York Heart Association (NYHA) classification showed 24 patients were in class I, seven in class II, 16 in class III, and three in class IV. Right ventricular endomyocardial biopsies were taken transvenously in all patients and samples were taken at the time of cardiac transplantation from the explanted heart of six patients. Biopsies were sectioned, stained with haematoxylin and eosin, and assessed by light microscopy with the Dallas criteria.[21] Due to the absence of diagnostic features on histology in dilated cardiomyopathy those biopsies in which there was fibrosis in the absence of an inflammatory cell infiltration were termed established dilated cardiomyopathy.

Controls

Seventy five myocardial control tissues were taken, mostly at the time of cardiac surgery, from patients with valvar disease (n = 19), coronary artery disease (n = 15), congenital heart disease (n = 2), or specific heart muscle disorders (hypertrophic cardiomyopathy (n = 3), cardiac amyloidosis (n = 1), right ventricular dysplasia (n = 1). Additional cardiac control tissue (n = 34) was taken at the time of coroners' necropsy from people who died suddenly. Although 12 of these deaths were due to myocardial infarction, 24 cases had no cardiac pathology and died from non-cardiac causes (violent deaths (n = 6); cerebrovascular accident (n = 5); carcinoma (n = 4); pulmonary embolism (n = 3); unknown (n = 6). Most samples were taken from the right ventricular septum.

ENTEROVIRAL SPECIFIC GENE AMPLIFICATION BY THE POLYMERASE CHAIN REACTION

The polymerase chain reaction is a recent development in molecular hybridisation technology, which enables a minute quantity of specific nucleic acid to be detected within a clinical sample after its extensive and selective amplification. In this assay total cellular ribonucleic acid was extracted from biopsy specimens and used to synthesise the more stable complementary deoxyribonucleic acid that is used in the subsequent polymerase chain reaction. With specially designed and enteroviral specific oligonucleotide primers, a region of the enteroviral complementary deoxyribonucleic acid was selectively amplified by the polymerase chain reaction. The amplified fragment of deoxyribonucleic acid then underwent gel electrophoresis and was transferred to a membrane that was hybridised with a radiolabelled enterovirus specific deoxyribonucleic acid probe and was then filmed by autoradiography.

Preparation of ribonucleic acid from myocardial samples

Endomyocardial samples were immediately snap frozen and stored in liquid nitrogen until required. Intact ribonucleic acid was extracted with RNAagents (Promega) from myocardial biopsy specimens by the one step procedure of Chomczynski and Sacchi.[22] Briefly, specimens were denatured and homogenised in guanidine thiocyanate with citrate/sarcosine/β mercaptoethanol buffer. Ribonucleic acid was extracted with phenol and chloroform and precipitated twice with isopropanol. The ribonucleic acid was then washed in 75% ethanol, vacuum dryed, and stored under 100% ethanol at −70°C until required. Before use these samples were centrifuged at 4°C and then resuspended in 10μl of RNAase free water. The quality of the ribonucleic acid was checked by northern blotting with a radiolabelled probe to actin and by absorbance spectrophotometry ($A_{260:280}$).

Preparation of coxsackievirus positive control ribonucleic acid

Coxsackievirus ribonucleic acid was prepared as a positive control from a stock of Coxsackie B3 virus (10^6 infectious agents/μl) harvested in phosphate buffered saline (PBS) from infected Vero cells when 50% of the cells exhibited cytopathic effects. Cells wee suspended in guanidine solution and ribonucleic acid was extracted as above.

Oligonucleotides

Enteroviruses show a high degree of nucleotide sequence homology and the oligonucleotides used in this assay have previously been shown to be highly specific for enteroviral genome and capable of detecting a broad range of enteroviruses.[23 24] The structures of this primer pair (E1 and E2) and the hybridisation probe E3 have been published previously and gene amplification has been shown to be enterovirus specific and produce a 196 base-pair fragment.[23]

Viral complementary deoxyribonucleic acid synthesis and the polymerase chain reaction
First strand complementary deoxyribonucleic acid synthesis and subsequent polymerase chain reaction gene amplification was performed with the Perkin-Elmer Cetus Gene-Amp Kit. First strand complementary deoxyribonucleic acid synthesis was achieved in a total volume of 20μl by random hexamers using 2μl of sample material and 50 U moloney murine leukemia virus reverse transcriptase. The final concentration of magnesium used was 3·75 mM. These mixtures were left at room temperature for 10 minutes, then incubated at 42°C for 15 minutes, 99°C for five minutes, and finally for five minutes at 5°C. The polymerase chain reactions were performed in a total volume of 100μl using 1U AmpliTaq (Perkin-Elmer Cetus) and 1μl each of a primer pair (E1 and E2, concentration 80 mg/ml) with a final magnesium concentration of 2·35 mM. The mixtures were incubated at 95°C for two minutes and then step cycled in a two temperature cycle with one minute at 95°C and one minute 60°C for 55 cycles and finally incubated for seven minutes at 60°C (Techne PHC-1). Amplified products were stored at −20°C until required. In each assay coxsackie virus positive samples and two negative samples, one with ribonucleic acid extracted from a normal myocardium and one containing no ribonucleic acid, were used as controls.

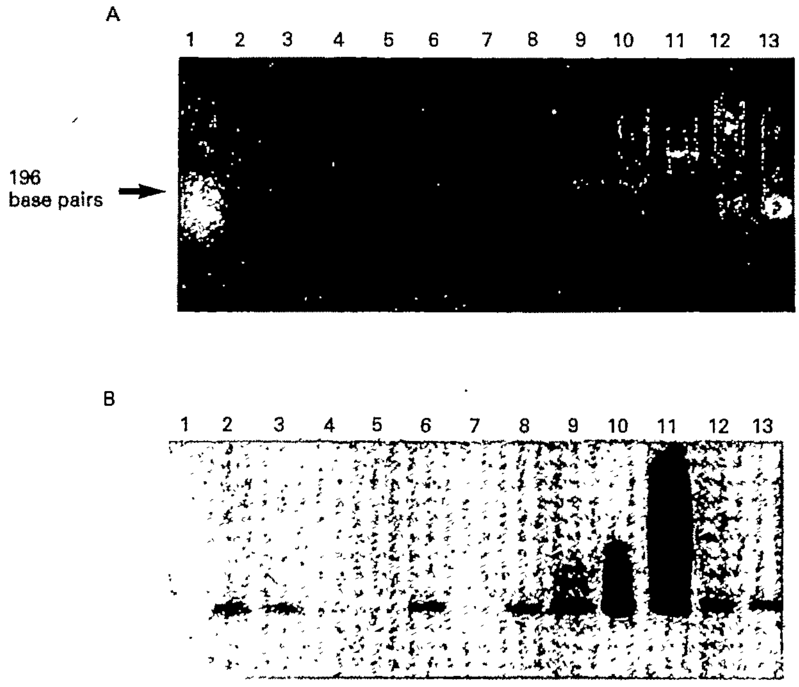

Figure (A) Agarose gel after electrophoresis of amplified product of polymerase chain reaction produced from myocardial samples from patients with dilated cardiomyopathy and controls. Clear bands are seen at 196 base pairs in most of the lanes of the gel except the negative control lanes. However in some lanes it is difficult to know whether a viral band is present or not (lane 1—a smear of nucleic acid obscures the region, lanes 11 and 12—faint bands may be present). Additional higher molecular weight bands produced from non-specific gene amplification can be seen in lanes 6 and 11. (B) corresponding autoradiographs after Southern blotting and hybridisation with radiolabelled E3 shows that the bands seen on the gel at 196 basepairs hybridise with E3, and are thus specific for enterovirus. The greater sensitivity of the assay after Southern blotting and hybridisation with radiolabelled E3 is confirmed by a hybridisation signal being produced in the apparent absence of a band on the gel (lanes 8, 11 and 12). Non-specific amplification products do not hybridise with E3 and are thus non-enteroviral. Non-specific hybridisation between E3 and cellular nucleic acid is shown as a smear of radioactivity in lane 11 and highlights one of the major limitations of slot blot hybridisation. Lane 1, negative control (Vero cell RNA); lanes 2–6, patients with dilated cardiomyopathy; lane 7, negative control (no RNA); lane 8, patient with valvar heart disease; lanes 9–11, victims of community sudden death; lanes 12, 13, patients with ischaemic heart disease.

Gel electrophoresis and Southern blotting
A total of 15μl of amplification product underwent electrophoresis at 100 V into 1·5% agarose gels in TBE (110g Tris, 55g boric acid/l, 20 ml 1 M EDTA). Gels were stained with ethidium bromide to detect deoxyribonucleic acid by illumination with ultraviolet light. The deoxyribonucleic acid was transferred to Hybond-N+membranes (Amersham) with 0·4 M sodium hydroxide as the alkali transfer buffer. One hundred ng of E3 was end labelled withγ^{32}P[ATP] by T4 polynucleotide kinase. Membranes were prehybridised for 30 minutes and hybridised for two hours at 37°C, in 10 ml 20× SSPE (3*M* sodium chloride, 0·18M sodium hydrogen phosphate, 0·018*M* EDTA), 2 ml 100× Denharts' solution (Ficoll 1%, polyvinylpyrrolidone 1%, bovine serum albumin 1%) and 2 ml 10% sodium dodecyl sulphate (SDS) made up to 40 ml in distilled water. The membranes were washed in 2 × SSC with 0·1% SDS at 50°C and then exposed overnight to an *x* ray film at −70°C with intensifying screens. To assess the sensitivity of the assay 10-fold serial dilutions of virus were prepared and 10^1 to 10^9 virons added to biopsy material from enterovirus negative myocardium. The ribonucleic acid from these specimens was then extracted with subsequent complementary deoxyribonucleic acid synthesis, polymerase chain reaction gene amplification, gel electrophoresis, and Southern blotting.

STATISTICAL ANALYSIS

Statistical analyses were performed with the Fisher's exact test with Yate's correction. Values are expressed as mean (SD) with $p < 0·05$ being considered significant.

Results

THE POLYMERASE CHAIN REACTION ASSAY

First strand complementary deoxyribonucleic acid synthesis with random hexamers produced more intense bands than did the use of the specific downstream primer (E1). The polymerase chain reaction had highly specific gene amplification with stringent annealing conditions, no extension cycle, and low enzme concentrations. This allowed completion of the large number of step cycles without undue non-specific gene amplification. Some assays with control tissue did produce non-specific gene amplification products. Further analysis of these samples showed that three to four times as much ribonucleic acid had been extracted and used in the assay and this non-specific gene amplification could be reduced with smaller amounts of ribonucleic acid in the assay. Gel electrophoresis of amplified product alone produced clear bands at 196 base pairs in 15 assays. Subsequent Southern blotting confirmed that these bands hybridised with radiolabelled E3. In some assays a significant degree of non-specific hybridisation with genomic ribonucleic acid and complemtary deoxyribo-

Table 1 Clinical features and results of enteroviral polymerase chain reaction in patients with dilated cardiomyopathy (mean (SD))

	Enteroviral genome	
	Positive	*Negative*
Number (n = 50)	6	44
Age (yr)	45 (16)	40 (12)
Duration of symptoms (months)	59 (58)	35 (49)
NYHA class (n)	I (3), III (3)	I (21), II (7), III (13), IV (−3)
Acute viral illness <6 months	1 (17%)	11 (25%)
LVEDD (mm)	69 (10)	68 (9)
LVEDD%	147 (17)	143 (20)
FS (%)	13 (9)	13 (7)
Histology*	Established 6	Established 21, normal 15, myocarditis 2, healing myocarditis 2

*According to Dallas criteria.
LVEDD, left ventricular end diastolic dimension; LVEDD%, percentage of calculated left ventricular end diastolic dimension (normal range <112%)[20]; FS, fractional shortening.

nucleic was found, but this could easily be distinguished from the specific band that hybridised at 196 base-pairs. Furthermore, after Southern blotting a positive hybridisation signal was obtained in four more assays in which no band had been seen initially after gel electrophoresis. The figure shows an agarose gel on which polymerase chain reaction amplified product from patients with dilated cardiomyopathy and control tissues has undergone electrophoresis (fig A), and the corresponding autoradiograph is also shown for direct comparison (fig B). To find the sensitivity of the assay serial dilutions of stock virus were added to biopsy samples and analysed as above. This showed that the assay was capable of detecting less than 10^2 infectious virions in each biopsy specimen.

PATIENTS WITH DILATED CARDIOMYOPATHY

Enteroviral genome was detected in 6/50 (12%) patients with dilated cardiomyopathy. Table 1 gives the clinical and biopsy features of these patients together with the results of the polymerase chain reaction assay. No differences in dilated cardiomyopathy paients with or without myocardial enteroviral genome were noticed in age, duration of symptoms, proportion of patients with a premorbid acute viral illness, excess alcohol consumption, hypertension, NYHA functional class, measures of left ventricular function, or results of endomyocardial histology. During follow up of the six patients with myocardial enteroviral genome, three patients remained unchanged at 7–25 (mean 18·7) months, one patient was improved at 27 months, one patient received an orthotopic heart transplantation at three months and one patient died suddenly at seven months. During the 2–52 (mean 22) month follow up of 44 patients without myocardial enteroviral genome, six died suddenly and nine received an orthotopic heart transplantation for progressive heart failure. Of the remaining patients 16 remained clinically stable (11 NYHA class I, five NYHA class II), nine had improved (NYHA class I) and two had deteriorated (one NYHA class II, one NYHA class III). No differences were noticed in the clinical outcome between those patients with and without enteroviral genome within the myocardium.

Table 2 Evidence from hybridisation studies of enteroviral involvement in human dilated cardiomyopathy and myocarditis

Author	*Hybridisation technique*	*Dilated cardiomyopathy n (%)*	*Myocarditis n (%)*	*Controls n (%)*
Peer review references:				
Archard *et al*[25]	Slot blot	35/82 (43)	21/47 (47)	0/39 (0)
Bowles *et al*[29]	Slot blot	6/21 (29)	—	1/19 (5)
Easton *et al*[33]	In situ	6/13 (46)	—	—
Grasso *et al*[14]	PCR	0/21 (0)	—	0/20 (0)
Jin *et al*[16]	PCR	3/20 (15)	2/28 (7)	0/ 9 (0)
Keeling *et al*	PCR	6/50 (12)	—	13/75 (17)
Tracy *et al*[32]	In situ	1/8 (12)	2/ 9 (22)	—
Weiss *et al*[28]	PCR	0/11 (0)	1/ 5 (20)	0/21 (0)
Non-peer review references:				
Kandolf *et al*[26]	In situ	8/47 (17) chronic 10/33 (30) recent onset		0/53 (0)

CONTROL PATIENTS

Enterovirus-specific gene amplification by polymerase chain reaction was noted in 13/75 (17·3%) of the control population. This was not significantly different when compared with the results of the dilated cardiomyopathy patients. Subgroup analysis showed the presence of myocardial enteroviral genome in 2/19 (10·5%) with valvar heart disease, 3/15 (20%) with ischaemic heart disease, 1/5 (20%) with specific heart muscle diseases, 0/2 (0%) with congenital heart disease, and 7/34 (20·6%) community sudden deaths including 3/12 (25%) cases who died from myocardial infarction.

Discussion

In this study we applied a highly sensitive and specific polymerase chain reaction technique to detect enteroviral genome in myocardial tissue taken from 50 patients with dilated cardiomyopathy and from 75 controls (41 with other forms of heart disease and 34 from coroners' necropsy cases). Enteroviral genome was detected within the myocardium in 6/50 (12%) patients with dilated cardiomyopathy but was not associated with any feature of clinical, histological, or functional assessment. Furthermore, the presence of enteroviral genome within the myocardium of these patients did not confer on them an adverse prognosis as has been proposed.[25] Our study also showed that enteroviral genome was present in myocardial tissues in a similar proportion of controls (17%).

All the patients studied with dilated cardiomyopathy have been extensively characterised with strict diagnostic criteria and are being regularly followed up. The control tissues were taken either at the time of cardiac catheterisation or surgery or from coroners' necropsies. The quality of the extracted ribonucleic acid, a particular concern for the necropsy tissues because of its possible degradation after death, was found to be adequate in all groups of patients. The polymerase chain reaction used in this study was highly sensitive and capable of detecting as few as 100 copies of enteroviral genome within a single endomyocardial biopsy specimen. The hybridisation probe (E3) used has previously been shown to be pan-enteroviral and capable of detecting a wide range of enteroviruses.[23]

Some non-specific hybridisation with genomic ribonucleic acid or complementary deoxyribonucleic acid was noted but this was easily distinguished from enteroviral specific hybridisation after gel electrophoresis and southern blotting of the amplification product.

We found enteroviral genome within the myocardium of 12% of patients with dilated cardiomyopathy: similar proportions were reported by other workers who used in situ hybridisation[15,26] or polymerase chain reaction techniques[16,27,28] but less than those reported by Archard *et al*[25,29] who used the technique of slot blot hybridisation (table 2). A limitation of slot blot hybridisation is non-specific hybridisation with genomic ribonucleic or deoxyribonucleic acid. This has been recently highlighted by Jin *et al*[16] who found that before gene amplification under conditions of low stringency, the extracted ribonucleic acid showed considerable non-specific hybridisation with a high number of false positive results. A further problem in several of the reported studies are the differences in selection of patients with dilated cardiomyopathy, and in particular to the presence of previous systemic hypertension or excess alcohol consumption. The finding of enteroviral genome within the myocardium of 17% of control tissues has not been reported. Previous studies, however, with sensitive and specific hybridisation techniques, have been limited in the number of control tissues analysed.[16,24] The only report that has assayed a significant number of control samples with in situ hybridisation has failed to detect enteroviral genome within the myocardium.[26] Whether this reflects the lower number of copies of enteroviral genome within the control tissues compared with those from patients with dilated cardiomyopathy due to the lower sensitivity of in situ hybridisation remains to be established.

Historically the principal supporting evidence linking enteroviral infection to dilated cardiomyopathy is derived from retrospective serological studies.[2,8,9] Infection with enteroviruses is common and infection with a single serotype often induces a multitypic response against several different serotypes with most people developing neutralising antibodies to a large range of serotypes early in adult life. Also there is usually considerable uncertainty in finding the time of the start of disease indilated cardiomyopathy as the preclinical phase of the disease is often very long. The introduction of specific assays for enteroviral immunoglobulin M promised to help with the identification of recent or persistent infection.[10] High levels of enterovirus specific immunoglobulin M have, however, also been reported in a number of other conditions including chronic relapsing pericarditis[10] and postviral fatigue syndrome[11] as well as in a matched control population taken from the community. Whether there is a difference in the prevalence or persistence of this enterovirus specific immunoglobulin M response between patients with dilated cardiomyopathy and a matched control population is not known at present. It is pertinent to remember that type I insulin dependent diabetes mellitus and amyotrophic lateral sclerosis were initially linked to enteroviral aetiologies on the basis of raised enteroviral serology, but subsequent studies with appropriate controls have failed to support this claim.[30,31] Also, a clear association between the presence of enteroviral specific immunoglobulin M and the presence of enteroviral genome within the myocardium has not been confirmed in patients with dilated cardiomyopathy.[32]

The significance of enteroviral genome within the myocardium in the small proportion of patients with dilated cardiomyopathy and its relation to active viral replication is unclear. Perhaps only active viral replication or infection with a particular type of enterovirus is responsible for the development of dilated cardiomyopathy, and this may only occur in patients with dilated cardiomyopathy and not the controls. Markers of active viral replication (for example enteroviral capsid protein, VP1) and the application of type specific enteroviral probes have not been assessed in dilated cardiomyopathy. Also the absence of a clear relation between the presence of viral genome and of histopathological damage within the myocardium has not been shown in humans by in situ hybridisation.[33] It is of course still possible that enteroviral infection may be important in pathogenesis of disease by acting as a trigger for the induction of autoimmunity as has been reported in the chronic form of murine myocarditis.[34–36] In this circumstance it would perhaps not be surprising with highly sensitive hybridisation techniques to find enteroviral genomic sequences in the absence of whole competent infectious viruses within the myocardium. The low prevalence of enteroviral genome, however, within the myocardium of patients with dilated cardiomyopathy and in a similar proportion of controls does not provide support for a pathogenic role of persistent enteroviral infection in dilated cardiomyopathy.

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Effect of exercise training on the total ischaemic burden: an assessment by 24 hour ambulatory electrocardiographic monitoring

Iain C Todd, David Ballantyne

Objective—**To examine the effect of prolonged high intensity exercise training on total ischaemic burden in men with chronic stable angina pectoris.**

Design—**A randomised controlled trial based on 24 hour ambulatory electrocardiographic monitoring of patients on two occasions a year apart.**

Setting—**Cardiology department of a large general hospital.**

Subjects—**40 men under 60 years of age with chronic stable angina pectoris and no previous myocardial infarction.**

Results—**After training the exercise group showed a 30% reduction in frequency of ST segment depression. There were significant reductions in painful episodes of ischaemia and those triggered by changes in heart rate. There was also a trend towards a reduction in silent ischaemia and episodes not triggered by changes in heart rate. The duration of ischaemic episodes was also reduced. No significant change in frequency or severity of dysrhythmia was shown.**

Conclusions—**Exercise training reduces total ischaemic burden in patients with angina pectoris by reducing the frequency and duration of all types of ischaemic episode.**

(*Br Heart J* 1992;68:560–6)

In a recent publication we reported the antianginal efficacy of exercise training compared with β blockade.[1] A brief daily exercise training regime was shown to compare favourably with daily atenolol when assessed by treadmill exercise tolerance. It is apparent, however, that the assessment of ischaemic heart disease and its treatment is incomplete without some measure of ischaemic activity outside the controlled environment of the exercise laboratory. The development of frequency modulated ambulatory electrocardiographic recording that allows accurate monitoring of ST segment changes has produced information that makes such monitoring vital not only in assessment of the disease but also the treatment.

Several authors have shown that most ischaemic episodes are not associated with pain.[1-5] Such silent episodes may relate to alterations in the pain threshold or to other as yet unidentified factors. They have the same characteristics as painful episodes and so may have the same clinical significance.[3 4] Most episodes of ischaemia on Holter monitoring, whether associated with angina or silent, are not secondary to increases in myocardial oxygen demand.[2-5] It is probable that they are secondary to alterations in myocardial oxygen supply. These facts raise two important aspects of the assessment of any treatment that can be clarified only by ambulatory electrocardiographic monitoring, namely the effect of treatment on silent ischaemia and the effect on ischaemia due to reduction in myocardial oxygen supply.

These areas have particular relevance to the question of the efficacy of exercise training in reducing angina. Exercise training has been shown to affect exercise induced increases in heart rate by reduction in sympathetic stimulation of the heart. If most episodes of angina are not induced by exercise then what effect can training have on these episodes? Furthermore patients on exercise training programmes report less angina and some become symptom free. Does this mean that they have fewer ischaemic episodes or have we merely changed them from painful to silent by raising their pain threshold or by increasing endogenous opiate production? To answer these questions we undertook a randomised controlled study of exercise training in men with chronic stable angina pectoris by 24 hour ambulatory electrocardiographic monitoring.

Patients and methods

Forty men under 60 years of age with chronic stable angina pectoris of at least six months duration and no previous myocardial infarction were recruited and allocated by a random number generator to exercise training and control groups. All had positive exercise tolerance tests by standard criteria with a treadmill. The demographic data and exercise tolerance results have already been published.[6] After randomisation the exercise group began the Canadian Airforce PBX plan of daily exercise training for physical fitness.[7] This programme consists of 11 minutes of daily callisthenic exercise and has already been described in detail.[6] Exercises were continued for a period of one year.

Holter monitoring was carried out with the Oxford Medilog 4000 (MARS) ambulatory electrocardiographic recorder. This frequency modulated recorder has a frequency response of 0·05–40 Hz and a signal to noise ratio of better than 30 dB. The recorder processes each

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complex in real time and stores the information on cassette tape. The information is later retrieved by playing the cassette through the Oxford Medilog MARS replay system. To ensure optimum quality, recorder heads were cleaned before each use and new batteries used for each recording. Cassette tapes were demagnetised before use. The patient's chest was shaved if necessary and the area of skin prepared by rubbing with abrasive paste to remove the stratum corneum. Electrodes were then applied to the chest over bony sites (fig 1). This produced a recording of leads CM5 and a modified lead II. An impedance meter was used to ensure that the resistance between electrodes was <5 k ohms. The leads were then attached to the patient with surgical tape incorporating stress loops to reduce artefacts. The whole electrode system was further fixed with an elastic vest and the recorder was worn in a pouch on a waist belt. A 1 mv calibration signal was fed into the recorder and an electrocardiographic signal recorded on a conventional machine to ensure adequate quality before starting to record. Two other channels recorded a quartz time signal and a flutter compensation signal during the 24 hours. Recordings were made among the exercise group at the end of the first week of the exercise regime timed in such a way that the patients could carry out their weekly supervised exercise before removal of the monitor. A repeat assessment was carried out one year into the exercise programme.

The control group underwent similar investigations one year apart. In the interim they were reviewed at three monthly intervals. No attempt was made to advise them either to undertake or to avoid exercise. Those patients who asked were told that moderate exercise may be of benefit. Medication for both groups during the study was nifedipine where required and if this was insufficient isosorbide dinitrate was also used. β blockers were not allowed during the study period. To ensure as far as possible that medication was not inadvertently changed, the control group were granted open access to the supervising physician.

The analysis of the completed 24 hour tapes was made up of two phases. Firstly the cassette was automatically analysed with the Oxford Medilog MARS replay system to produce trend graphs of heart rate, ST segment analysis, and ventricular extrasystoles. Also an hourly summary of maximum and minimum heart rates and arrhythmias was produced. The second phase of the analysis was to use the summary information to select times of ST segment shift or arrhythmia, and by entering these times in the replay system. Print outs of the two lead electrocardiograms were obtained. This manual check meant that all events identified were confirmed as genuine and in no case was the diagnosis of ST segment depression or arrhythmia based solely on software used by the automatic analysis programme. This was particularly important with regard to ST segment analysis as the starting point of onset of ST depression could be accurately identified, the heart rate at that point could be measured, and the change in heart rate over the preceding minute could also be ascertained.

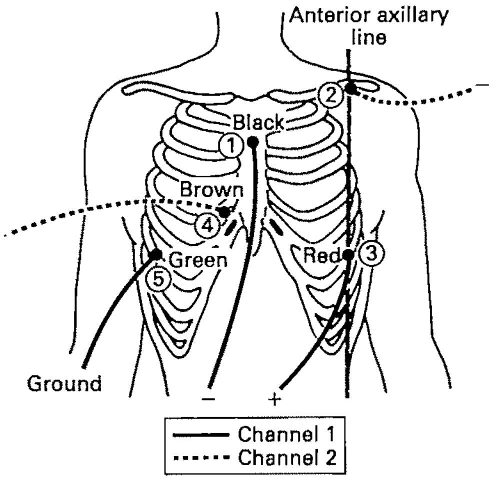

Figure 1 Lead positions for ambulatory electrocardiography. Electrodes 1 and 3 provide OM5 recording and electrodes 2 and 4 record lead I.

Significant ST segment depression was defined as horizontal or downsloping shift of $\geqslant 1$ mV from a baseline occurring 80 ms after the J point and lasting for at least 30 s. Patients with obvious resting ST segment or T wave changes in the monitored lead were excluded from analysis. Ventricular extrasystoles or arrhythmic activity was analysed as the total number of ventricular premature contractions per hour or per 24 hour period and as the maximum Lown grading of ventricular extrasystoles noted on the patient's tape.[8] Table 1 shows the Lown grading system.

STATISTICAL ANALYSIS

Data relating to heart rates were normally distributed and therefore a Student's paired *t* test was used for intragroup analysis. ST segment data did not conform to a normal distribution, and these data were therefore analysed with the Wilcoxon signed rank test as were the data for total ventricular extrasystoles. As both periods of monitoring were carried out after randomisation and the exercise group included periods of exercise, intergroup comparison was inappropriate.

Results

There were no significant differences between the groups at baseline in terms of demographic data or drug treatment. Nifedipine was used for symptomatic control in most cases at the outset. Three patients found it unhelpful and one of these used isosorbide dinitrate instead. At the end of the study most of the exercise group were symptomatically improved such that eight had discontinued medication. Three of

Table 1 Lown ventricular extrasystolic grading system[8]

Grade 0	No VPCs
Grade 1A	Occasional isolated VPCs (<30/h) <1/min
Grade 1B	Occasional isolated VPCs (>30/h) <1/min
Grade 2	Frequent VPCs (>30/h)
Grade 3	Multiform VPCs
Grade 4A	Repetitive VPCs; couplets
Grade 4B	Repetitive VPCs; salvos
Grade 5	Early VPCs (R on T)

VPCs, ventricular premature contractions.

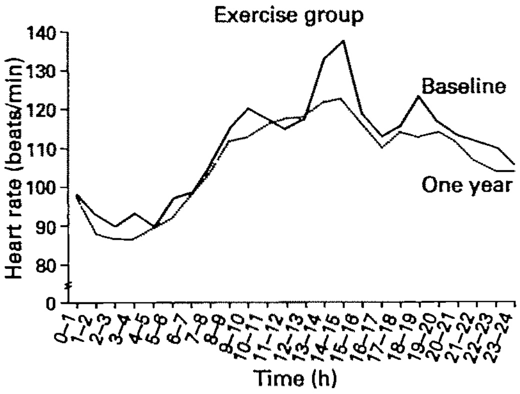

Figure 2 Maximum 24 hour heart rates in the exercise group.

the control group increased the dose of nifedipine and one added oral nitrates.

Compliance among the exercise group was high as assessed by continued attendance at hospital supervised sessions and the ability to perform exercises well. Only one patient in the exercise group defaulted, one other was withdrawn due to unstable angina, and one was not able to attend for repeat assessment. Of the 17 who were restudied all reported increased levels of physical activity in diaries recorded while wearing the tape, including return to work and participation in daily walking or sporting activities. The tape results at one year therefore represent recordings at higher activity levels on fewer antianginal drugs.

By contrast there were no significant changes in activity among the controls. Two patients defaulted from follow up, one died suddenly, one was unable to tolerate the tape on either occasion and two refused repeat taping, leaving 14 completed controls.

Figure 2 shows the hourly maximum heart rate for the exercise group at baseline and one year. For this, as well as for minimum and mean heart rate, there was a trend towards lower heart rates after exercise training. Individual results were, however, variable and the standard deviations large, so the differences were not significant. Table 2 shows the group means for minimum, maximum, mean, and nocturnal heart rate. The mean heart rate was calculated by dividing the total number of beats/24 hours by 1440. The mean nocturnal heart rate was calculated by averaging the mean hourly heart rates over six consecutive hours while the patient was asleep, the six hour group chosen being that group studied between midnight and 8.00 am that produced the lowest mean heart rate. Again the trend for all four measurements was towards a reduction in heart rate after exercise training. The reductions in minimum 24 hour heart rate and mean 24 hour heart rate were not significant. Maximum heart rate (mean (SD)) was significantly lower after training at 142 (16·1) compared with 151 (17·8) at baseline (p <0·05). Mean nocturnal heart rate was also significantly lower after training at 63 (4·6) compared with 66 (6·3) before training (p < 0·04). All heart rates measured in the control group tended to increase at one year compared with baseline, although none was significant.

Table 2 Mean (SD) group 24 hour heart rates

	Exercise group			*Control group*		
Heart rate	*Baseline*	*One year*	*p Value*	*Baseline*	*One year*	*p Value*
Minimum	50 (5·3)	48 (4·0)	NS	49 (5·8)	51 (6·4)	NS
Maximum	151 (17·8)	142 (16·1)	<0·05	137 (14·6)	139 (18)	NS
Mean	81 (8·4)	79 (6·7)	NS	79 (6·8)	80 (7·0)	NS
Nocturnal	66 (6·3)	63 (4·6)	<0·05	66 (9·1)	69 (7·8)	NS

Table 3 shows the individual results for maximum ST segment depression, frequency of ST segment depression, and total duration of ST segment depression in addition to group means, standard deviations, and p values (Wilcoxon signed rank test). Maximum ST segment depression in the exercise group at baseline ranged from 0 to 6 mm with a mean maximum ST segment depression of 2·2 mm. This was reduced by 30% after training to 1·5 mm (range 0–3·8 mm, p = 0·04). This improvement is reinforced by a reduction in frequency of ST segment depression from 8·3 to 5·2 episodes/patient/24 hours (p = 0·02). The total duration of ST segment depression was also reduced from 63·7 to 37·7 min/24 hours (p = 0·02). Over the same period the control group showed no significant change in any of these measurements.

Tables 4 and 5 show the characteristics of the episodes of ST depression. The total number of episodes of ST depression in the exercise group was reduced by 37%. Of the initial 141 episodes, 23% were associated with pain as reported by the patients in diaries. At one year only 12% of the 89 episodes was painful. Mean number of painful episodes of ST depression had therefore decreased from 1·9 (1·9) to 0·7 (1·0) (p = 0·02). There were 108 silent episodes at baseline and 77 at one year, representing a mean frequency of 6·4 (7·6) episodes/patient at baseline and 4·5 (7·0) at one year. This difference however was not significant. In the control group there were 80 episodes of ST depression at baseline and 88 at one year, 24% were painful initially and this had decreased to 12% at one year. The reduction in painful episodes was accompanied by an increase in silent episodes. There was no significant change in the mean frequency of either painful or silent episodes in the control group.

The episodes can also be subdivided into those with an increase in heart rate of >six beats/min during the minute preceding the onset of ST depression (heart rate triggered) and those not so associated. In the exercise group there were 79 heart rate triggered episodes at baseline and 45 at one year, representing a frequency of 4·6 (4·6) at baseline and 2·6 (3·5) at one year (p = 0·008). The incidence of events not triggered by heart rate also fell from 3·6 (4·9) (62 events) to 2·6 (3·9) (44 events). This reduction, however, failed to achieve statistical significance. In the control group there was no significant change in mean frequency of either heart rate triggered or non-heart rate triggered episodes. Figure 3 is a frequency histogram of duration of ischaemic episodes showing that at baseline there was a fairly even distribution of frequency of episodes in the four bands up to 30 minutes

Table 3 Individual characteristics of ST segment depression

	Maximum		*Frequency*		*Total duration*	
Patient no	*1*	*2*	*1*	*2*	*1*	*2*
			Exercise group			
1	1·0	1·8	1	2	4	2
2	1·5	1 0	4	3	30	7
3	3 2	1·0	17	1	122	4
4	0	0	0	0	0	0
5	2·6	0	1	0	3	0
6	4·6	1·0	13	1	95	2
7	1·0	1·0	1	1	2	2
8	3·0	3·4	15	15	117	91
9	0	0	0	0	0	0
10	2·0	1·5	6	9	25	150
11	2·2	2·5	14	11	163	96
12	1·3	1·0	8	3	52	11
13	6·0	3·8	13	12	197	97
14	1·4	1·1	1	1	3	1
15	2·2	2·0	17	4	60	10
16	2·8	1·0	3	1	12	1
17	3·0	3·2	27	25	198	167
Mean (SD)	2·2 (1·5)	1·5 (1·2)	8·3 (8·0)	5·2 (7·0)	63·7 (71·2)	37·7 (57·8)
p Value	0·04		0·02		0·02	
			Control group			
21	1·0	1·8	6	13	8	56
22	2·5	2·8	10	11	45	44
23	1·2	1·2	6	6	22	22
24	1·4	0	1	0	6	0
25	3·5	3·8	21	30	296	254
26	1·5	0	7	0	102	0
27	0	0	0	0	0	0
28	0	1·6	0	1	0	3
29	1·0	1·0	1	1	5	5
30	1·9	1·8	15	11	139	68
31	1·0	1 0	1	4	3	12
32	2·0	2·3	7	11	65	165
33	2·5	0	5	0	32	0
34	0	0	0	0	0	0
Mean (SD)	1·4 (1·0)	1·2 (1·2)	5·7 (6·2)	6·3 (8·5)	51·6 (82·2)	44·9 (75·4)
p Value	NS		NS		NS	

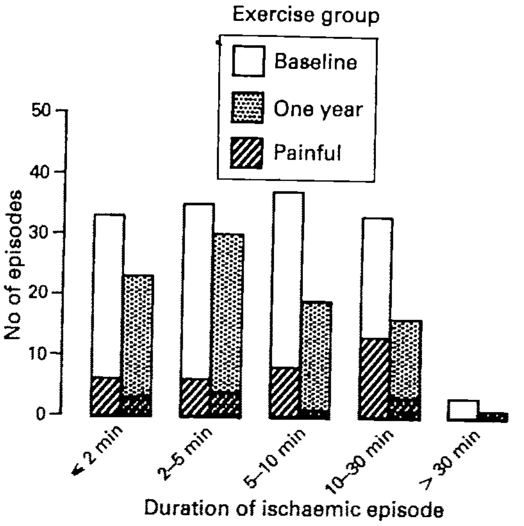

Figure 3 Frequency histogram of duration of ischaemic episodes at baseline and at one year in the exercise group.

duration. At one year, however, there was a relative reduction in frequency of episodes over five minutes duration. Therefore not only were there fewer episodes, but those episodes that did occur tended to be shorter. These two facts together account for the reduction in total duration of ischaemic time. Figure 4 is a similar histogram for the control group showing consistency over the one year period.

The mean heart rate at the onset of ST segment depression, mean maximum heart rate during ST segment depression, and mean maximum degree of ST segment depression/episode were all unchanged in either group over the one year period.

Figures 5 and 6 show the hourly total number of ventricular premature contractions for the two groups; both groups show an increased frequency at one year. Although the total number of ventricular premature contractions increased greatly in each group, these increases were accounted for by one or two patients in each group and the mean change was not statistically significant. Table 6 shows the maximum Lown grading achieved by each patient. At baseline only six of 17 patients in the exercise group had a Lown grading ≥2. At one year seven patients were ≥ grade 2. In the control group only two of the 14 patients were ≥ grade 2 at baseline and three at one year. Five patients in the exercise group had identical Lown gradings on both occasions, whereas seven had improved grading and five were graded worse at one year. Among the controls 10 patients showed no change, one improved, and three became worse.

Discussion

There are no previous studies on ambulatory monitoring during exercise training with which to compare these results. The technique has, however, been used to assess drug treatment in angina pectoris and one can therefore compare the antianginal efficacy of exercise training with drugs in these studies.[9–12] The reduction in hourly heart rate is perhaps less than might have been expected after training. It was clear, however, that most patients with angina were, on medical advice, relatively sedentary patients at baseline and by the end of the year this trend had largely been reversed and they were encouraged to be physically active as often as possible. It is likely therefore that the expected reduction in mean heart rate had been offset by an increase in physical activity. The resting bradycardia of the athletic person is evident,

Table 4 Characteristics of episodes of ST segment depression in the exercise group

	Baseline			*One year*			
	Group total	*(%)*	*Mean (SD)*	*Group total*	*(%)*	*Mean (SD)*	*p Value*
All episodes	141	100	8·3 (8·0)	89	100	5·2 (7·0)	0·02
Painful	33	23	1·9 (1·9)	12	13	0·7 (1·0)	0 02
Silent	108	77	6·4 (7·6)	77	87	4·5 (7·0)	NS
HR triggered	79	56	4·6 (4·6)	45	51	2·6 (3·5)	0·008
Non HR triggered	62	44	3·6 (4·9)	44	49	2·6 (3·9)	NS
Mean HR at onset of ST depression	—	—	107 (17)	—	—	106 (14)	NS
Maximum HR during ST depression	—	—	116 (19)	—	—	112 (16)	NS
Mean maximum degree of ST depression	—	—	1·8 (0·9)	—	—	1·6 (0·7)	NS

Table 5 Characteristics of episodes of ST segment depression in the control group (p values all non-significant)

	Baseline			*One year*		
	Group total	*(%)*	*Mean (SD)*	*Group total*	*(%)*	*Mean (SD)*
All episodes	80	100	5·7 (6·2)	88	100	6·4 (8·4)
Painful	19	24	1·4 (1·8)	12	14	0·9 (2·0)
Silent	61	76	4·4 (5·8)	79	86	5·4 (8·3)
HR triggered	47	59	3·4 (4·4)	59	67	4·2 (6·2)
Non HR triggered	33	41	2·4 (2·8)	29	33	2·1 (2·9)
Mean HR at onset of ST depression	—	—	101 (11)	—	—	103 (11)
Maximum HR during ST depression	—	—	114 (12)	—	—	114 (14)
Mean maximum episodic ST depression	—	—	1·5 (0·5)	—	—	1·7 (0·7)

however, in a significant reduction in nocturnal heart rate implying an increase in resting vagal tone. The graphs of maximum heart rate also provide evidence of the training effect if the heart rates between 2 and 3 pm on the two occasions are compared. This corresponds to the peak heart rate during the exercise class and has been significantly reduced after training despite a much higher level of exercise. Likewise the group maximum heart rate decreased from 151 to 142 bpm despite the overall increase in physical activity. These measurements support the belief that the improvements in response of heart rate to exercise are not confined to treadmill measurements but do genuinely carry over into normal daily activities.

The baseline measurements for the exercise group show a rather higher maximum ST segment depression and higher mean frequency of ST segment depression than the control group. One must remember, however, that this test was carried out after the start of exercise training. Most subjects performed their exercises on two occasions during the 24 hour period (before retiring to bed or on rising from it and at the exercise class). In most cases this represents two deliberate episodes of provoked ischaemia accounting for most of the difference in mean baseline frequency of ST segment depression between the groups (8·3 *v* 5·7). As in many cases maximum ST segment depression occurred during the exercise routine this also partly explains the difference in maximum ST segment depression (2·2 *v* 1·4). These facts aside, however, the change within the exercise group over the one year period is striking, again considering the apparent increase in physical activity. Not only has maximum ST segment depression decreased, but also the frequency and duration have been reduced; and the frequency histogram also shows that episodes of ST segment depression tend to be of shorter duration. The antianginal effect of the training programe previously shown on the treadmill is also clear during ambulatory monitoring. There are fewer episodes and those that do occur are shorter and less severe so that total ischaemic burden is reduced. The argument that encouraging such physical activity in the presence of ischaemic heart disease may be dangerous by actively provoking myocardial ischaemia is somewhat weakened in this context as paradoxically we have reached a situation where there is less ischaemia despite an increased physical activity. The reverse side of the coin must also be true however. If the hypothesis that provoking ischaemia is effective as a means of improving collateral blood flow is true then we have also reached a situation where those in the control groups at the end of one year are being stimulated more than the exercise group. To maintain the stimulus to improve perfusion it may be necessary, therefore to increase exercise duration and intensity further.

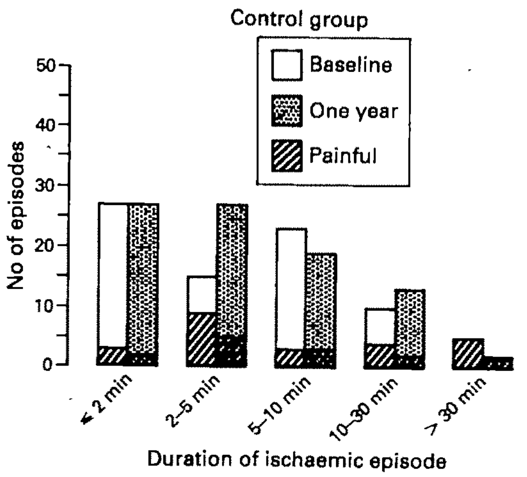

Figure 4 Frequency histogram of duration of ischaemic episodes at baseline and at one year the control group.

The antianginal efficacy of exercise training as measured by ambulatory electrocardiographic monitoring is comparable to that with drug treatment. Quyyumi *et al* studied a group of patients with severe angina pectoris whose baseline measurements of ST depression were similar to the group studied here in terms of frequency, duration, and extent of ST depression and incidence of painful and silent ischaemia.[9] They were treated with atenolol and pindolol in a double blind crossover study. Pindolol decreased the frequency of ischaemic episodes by 30%, whereas atenolol produced a reduction in frequency of 53%. Duration of ischaemia was reduced by 30% with pindolol and 45% with atenolol, figures not dissimilar to those produced by the exercise group studied here. Studies with calcium antagonists show similar degrees of efficacy,[10–12] although interestingly, nifedipine, the drug used as an antianginal treatment in this study, seemed not to decrease frequency or extent of ST depression in the study of Bala Subramanian *et al.*[12]

One of the major discoveries resulting from the use of ambulatory ST segment monitoring is that the typical painful ischaemic episode of ST segment depression provided by changes in heart rate is very much in the minority, most episodes of ST segment depression being painless.[4 5 13 14] Also most are not triggered by an increase in heart rate.[5 13 15] We postulated that exercise training might, by increasing

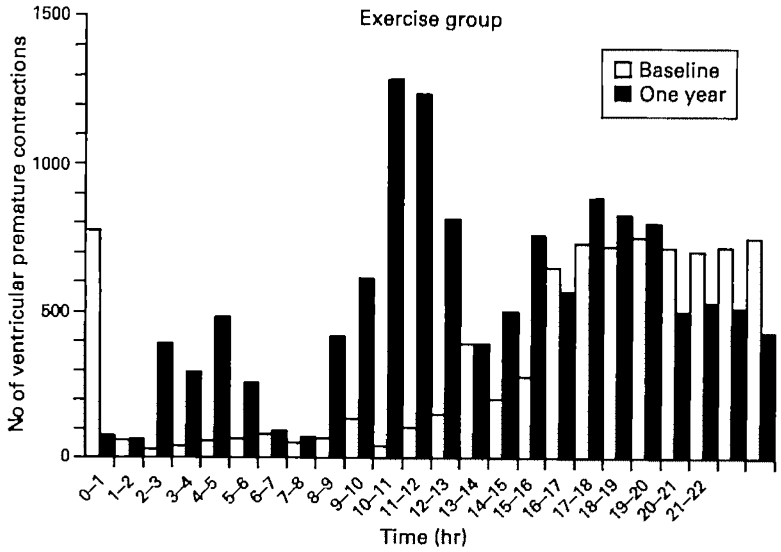

Figure 5 Frequency histogram of hourly ventricular premature contractions in the exercise group.

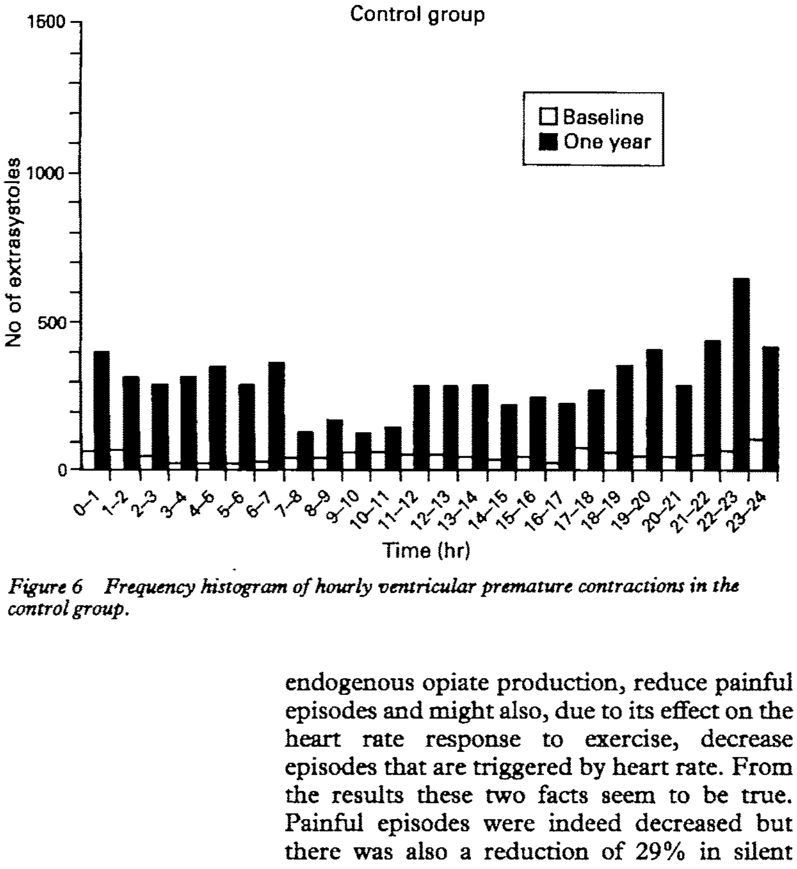

Figure 6 Frequency histogram of hourly ventricular premature contractions in the control group.

Table 6 Lown grading of ventricular extrasystoles at baseline and one year

	Exercise group		Control group	
Lown grade	*Baseline (n)*	*One year (n)*	*Baseline (n)*	*One year (n)*
0	0	2	1	0
1A	10	7	11	11
1B	1	1	0	0
2	3	3	0	1
3	1	1	0	1
4A	0	1	1	1
4B	1	2	1	10
5	1	0	0	0

endogenous opiate production, reduce painful episodes and might also, due to its effect on the heart rate response to exercise, decrease episodes that are triggered by heart rate. From the results these two facts seem to be true. Painful episodes were indeed decreased but there was also a reduction of 29% in silent episodes that was not significant. This would suggest that the primary effect on the exercise group was a reduction in ischaemia, and that superimposed on this was the tendency for fewer episodes to be recognised by the patient, whether due to opiate production or denial. In the control group, on the other hand, whereas painful episodes did decrease, silent episodes increased. Although neither change was significant it is clear that there was no overall decrease in ischaemia but a tendency to report pain less often.

In the exercise group the situation for events triggered by heart rate or non-triggered events was similar. Both were reduced but only the events triggered by heart rate were significantly reduced. Whereas the reduction in episodes triggered by heart rate is to be expected in a trained subject, any reduction in the rate of non-triggered episodes is encouraging and one would like to see this trend studied in a larger group.

Interestingly, despite the improvements outlined above there was no reduction in the mean heart rate at the onset of ST segment depression, mean maximum heart rate during ST segment depression, or mean maximum ST segment depression. There seems, therefore, to be no change in the threshold for ischaemia to suggest an improvement in myocardial perfusion. This contrasts with the treadmill results in this group where maximum heart rate and ST threshold were increased. As usual with ambulatory monitoring, however, the heart rate thresholds are low indicating that increases in heart rate are only part of the equation even in the episodes triggered by heart rate. These figures perhaps reflect the variability of other factors in the ischaemic process and the lack of sensitivity of ambulatory ST segment monitoring compared with treadmill exercise testing.

The monitoring of arrhythmias was always likely to be beyond a study of this sort. Whereas early studies suggested that premature ventricular contractions were important indicators of risk of sudden death,[16 17] it has been recognised that there is a great variation in the occurrence of arrhythmias during ambulatory monitoring[8] and that as episodes in Lown class I are common, they are therefore poor discriminators for identifying patients at risk of sudden death.[18 19] More complex arrhythmias, on the other hand, do seem to predict sudden death but are much more variable in their occurrence and overall are less common.[18 20] A small group such as this would inevitably produce too few serious arrhythmias and those produced would become irrelevant in the context of natural variability in their occurrence.[21] Training produced no evidence of a reduction in extrasystoles and little change in the more serious arrhythmias with roughly one third improved, one third worse, and one third unchanged. Whether these arrhythmias are more or less likely to be associated with sudden death in the trained patient is perhaps the key question but beyond the scope of this study. In view of concern over the question of the value of exercise training in preventing sudden death this question would merit further study.

In summary, this study has shown a reduction in frequency and duration of angina and ischaemia after training as assessed by ambulatory monitoring. Whereas the changes are significant only for episodes that are painful or triggered by changes in heart rate, there is a trend towards a reduction in silent ischaemia and that not triggered by heart rate. This trend may have been significant had we studied larger numbers or extended the study period to 48 hours of monitoring, which is now the accepted norm. This aside, daily exercise training in this group at least would seem an effective way of reducing the total ischaemic burden in angina pectoris.

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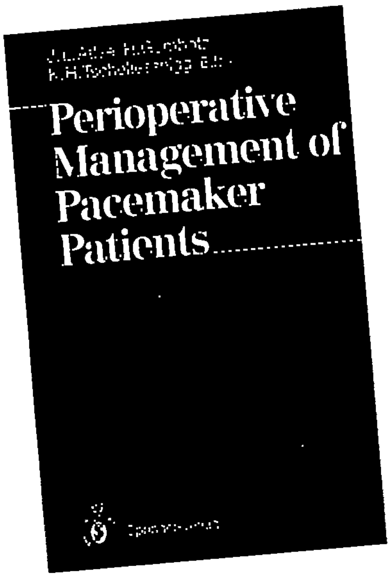

J. L. Atlee III, Milwaukee, WI;
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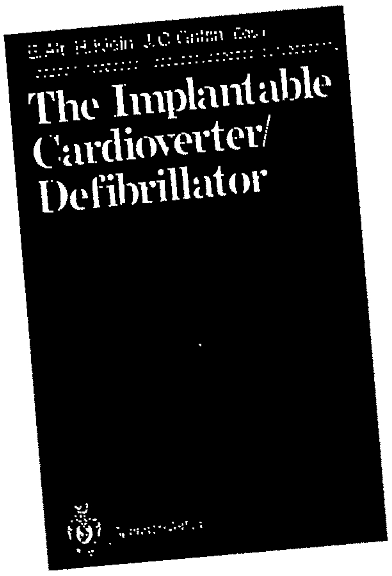

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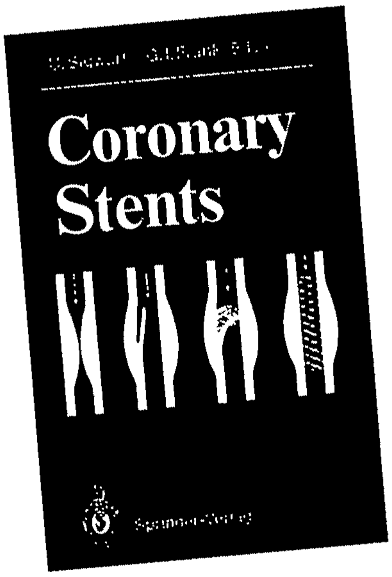

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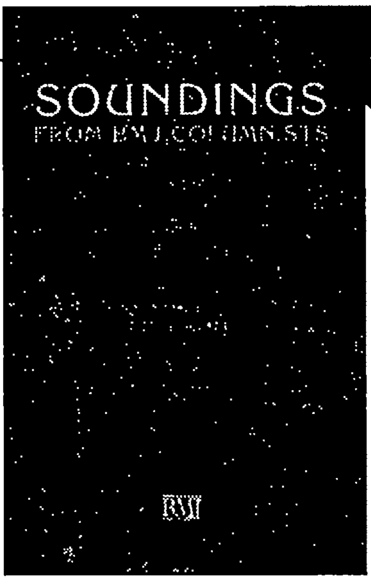

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Relation of left ventricular isovolumic relaxation time and incoordination to transmitral Doppler filling patterns

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Abstract

Objective—To investigate factors during isovolumic relaxation that determine Doppler filling patterns in patients with left ventricular disease, and thus to identify the underlying mechanisms.

Design—85 patients (50 ischaemic heart disease, 35 left ventricular hypertrophy due to aortic stenosis) and 26 controls were studied with Doppler and M mode echocardiography and phonocardiography. 16 patients underwent two studies on separate occasions, to find whether changes in isovolumic relaxation time were reflected by a change in the Doppler A/E ratio.

Setting—A tertiary cardiac referral centre.

Subjects—Patients referred for assessment of coronary artery disease or aortic stenosis with left ventricular hypertrophy.

Main outcomes measures—Doppler filling velocities during early (E wave) and late (A wave) diastole and the A/E ratio, acceleration of the E wave, digitised M mode indices of incoordinate relaxation (change in cavity dimension before mitral valve opening and time from minimum dimension to mitral valve opening), isovolumic relaxation time, M mode measures of diastolic function after mitral valve opening (peak rate of posterior wall thinning and peak rate of dimension increase), and left ventricular end diastolic pressure.

Results—A/E correlated with age in normal subjects ($r = 0·74$), to a lesser extent in left ventricular hypertrophy ($r = 0·41$), but not significantly in ischaemic heart disease. In all patients, isovolumic relaxation time was significantly and negatively correlated with the acceleration of the E wave, showing its fundamental relation to the force responsible for early diastolic filling ($r = -0·71$ for left ventricular hypertrophy, and $-0·74$ for ischaemic heart disease, p value $< 0·01$). In left ventricular hypertrophy and those ischaemic patients without left ventricular dilatation A/E was correlated both with isovolumic relaxation time ($r = 0·68$ and $0·60$ respectively), and with incoordinate relaxation ($r = 0·65$ and $0·61$). In those ischaemic patients with left ventricular dilatation, the influence of incoordination was lost and isovolumic relaxation time became the dominant influence upon A/E ($r = 0·82$). Weak correlations of end diastolic pressure and RR interval with A/E, became insignificant once isovolumic relaxation time had been taken into account. Isovolumic relaxation time and incoordination together accounted for over 50% of the variance in the A/E ratio in our patients. Isovolumic relaxation time and the A/E ratio were linearly related. Patients with a short isovolumic relaxation time had evidence of considerable diastolic abnormalities, despite a normal Doppler A/E ratio. In the 16 patients who had two echocardiographic studies, changes in the duration of isovolumic relaxation were accompanied by a change in the Doppler A/E ratio. The relation between these two variables, derived from the group as a whole was similar.

Conclusions—The main factors influencing the A/E ratio in patients with left ventricular disease are two distinct properties of isovolumic relaxation—namely the duration and the extent of incoordinate wall motion. Filling pressure and RR interval are not significant independent determinants, but act only through an effect upon isovolumic relaxation time. Age is an important influence in normal people, but this effect is attenuated in left ventricular hypertrophy and lost in ischaemic ventricular disease.

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The pattern of diastolic inflow into the ventricle can be conveniently studied with pulsed Doppler echocardiography, and the ratio of peak atrial to early diastolic velocities (A/E ratio) has been used by many as an index of underlying left ventricular diastolic disease.[1,2] Yet the precise mechanisms responsible for filling are complex and incompletely understood. In normal individuals, age is well recognised to be the primary determinant of the A/E ratio,[3-5] although in disease states it is likely that this effect will be attenuated by other overriding factors. As blood flow velocity is a function of transmitral pressure gradient, relations with left atrial or left ventricular end diastolic pressure have been sought and not surprisingly have been found. In different studies, however, the correlation of the early filling velocity and E/A with filling pressure, has been reported to be positive,[6-8] negative,[9] and non-existent,[10] although striking changes in filling velocities due to acute alteration of loading conditions have been documented both in animals,[11] and patients.[12 13] Disturbances of the A/E ratio and peak rapid filling velocity have been ascribed to abnormal relaxation,[14-16] as well as to reduced atrial and ventricular compliance,[2 17 18] whereas M mode studies have shown that in left ventricular hypertrophy, the A/E ratio may be normal in the presence of obvious diastolic disease.[19] Our study is based on previous findings that the duration of isovolumic relaxation or the rate of left ventricular pressure decline may affect early diastolic filling velocity in patients with left ventricular hypertrophy[19 20] or ischaemic heart disease.[21] It was our aim to assess the extent to which filling velocities depended on events occurring before mitral valve opening, to identify the factors during isovolumic relaxation that might be responsible, and thus to gain insight into underlying mechanisms.

Patients and Methods

STUDY POPULATION

We studied 50 patients (42 men, eight women, mean age (range) 59 (37–81) years) with ischaemic heart disease, 35 patients with left ventricular hypertrophy secondary to aortic stenosis (20 men, 15 women, mean age 56 (14–82) years), and a control group of 26 healthy individuals (18 men, eight women, mean age 49 (20–82) years). All patients had been referred for echocardiographic evaluation of ventricular function. Cardiac catheterisation and measurement of end diastolic pressure were carried out in 52 patients as part of their routine assessment.

M MODE AND CROSS SECTIONAL ECHOCARDIOGRAPHY

M mode and cross sectional echocardiograms with an Advanced Technical Laboratory Imager Mk 300I with a 3·0 MHz mechanical transducer, or a Toshiba SSH 160A imager with a 3·5 MHz transducer were taken with the patient in the standard left lateral position. Phonocardiograms were recorded with a Leatham microphone with a low frequency filter. M mode echocardiograms were recorded with simultaneous eletrocardiogram and phonocardiogram, on a Honeywell (Ecoline 22) strip chart recorder at a paper speed of 10 cm/s. Only records showing clear continuous echoes from the septum and posterior wall and clear mitral cusp separation were used. Aortic valve closure (A_2) was taken as the start of the first high frequency vibration of the aortic component of the second heart sound recorded on the phonocardiogram, and was checked for validity with the aortic echogram and the aortic closure artefact on the Doppler recordings. Left ventricular internal cavity dimensions were measured at end systole (A_2) and end diastole (start of the QRS complex on the electrocardiogram) with leading edge method, from the parasternal long axis view. Isovolumic relaxation time was measured from A_2 to the initial separation of the mitral cusps on the M mode echogram. All measurements were made on three cardiac cycles and the mean taken. M mode echocardiograms were digitised with a Terminal Display Systems TDS 20 digitising tablet as previously described.[22] Measures of incoordinate relaxation were taken as the increase in transverse cavity dimension during isovolumic relaxation expressed as a percentage of the total dimension change during the cardiac cycle, and the time interval from minimum cavity dimension to mitral valve opening. The peak rate of dimension increase (dD/dt), and the peak rate of posterior wall thinning (dW/dt) were also derived from the digitised traces. Once again, all measurements were made on three cardiac cycles, and the mean taken.

DOPPLER ECHOCARDIOGRAPHY

We recorded Doppler signals with a Doptek Spectrascan and a 2·0 MHz transducer, and a Toshiba SSH 160A with a 3·5 MHz transducer. Peak transmitral flow velocities were identified by continuous wave from the apex, and were recorded in pulsed mode with a 3 mm gate, and 250 MHz wall filter. The peak velocities of early E wave and atrial A wave transmitral flow were recorded and the A/E ratio was calculated. The time from onset of early transmitral flow to the peak velocity was taken as acceleration time, and the peak velocity divided by acceleration time as early diastolic acceleration. The time interval of aortic closure to the onset of transmitral flow was also recorded. Records were taken with simultaneous electrocardiogram and phonocardiogram at a paper speed of 10 cm/s. All measurements were made on three cardiac cycles and the mean taken.

CARDIAC CATHETERISATION

52 patients from the two study groups underwent cardiac catheterisation as part of their routine assessment, from either the brachial or femoral approach. Pressure was recorded before left ventricular angiography with a fluid filled 7 or 8 French pigtail catheter attached to a manifold micromanometer transducer (Medex Medical), with zero taken at mid-chest level. The left ventricular end diastolic pressure was measured at the point on the pressure waveform corresponding to the onset of the QRS complex on the electrocardiogram. The mean of 10 cardiac cycles was recorded. All studies were performed within 48 hours of the echocardiographic examination.

STATISTICAL ANALYSIS

All values are given as mean (SD). Differences between mean values were compared by Student's *t* test. Simple and stepwise regression, multiple regression, and linear correlation were performed to assess relation between variables.

Results

GROUP CHARACTERISTICS

Table 1 summarises the description and comparison of the subjects. The patients with ischaemic heart disease were older than the normal subjects, but no other significant dif-

Table 1 Characteristics of the groups (mean (SD))

	Ischaemic heart disease (n = 47)	*Left ventricular hypertrophy (n = 35)*	*Controls (n = 26)*
Age (y)	59 (9)†	56 (19)	49 (17)
LVEDD (cm)	5·9 (1·1)*†	4·8 (1 0)	5·0 (0·6)
RR interval (ms)	800 (200)†	835 (140)†	930 (155)
A wave velocity (m/s)	0·43 (0·29)*†	0·68 (0·3)†	0·54 (0·12)
E wave velocity (m/s)	0·71 (0·20)*	0·86 (0·31)†	0·69 (0·17)
E wave acceleration (m/s²)	11·7 (6·0)	9·3 (4·6)	11·4 (3·1)
A/E ratio	0·72 (0·60)	0·87 (0·49)	0·79 (0·28)
Isovolumic relaxation time (measured to mitral valve opening) (ms)	60 (35)	60 (25)	60 (10)
Aortic closure to start of transmitral flow (ms)	105 (40)	85 (30)	85 (10)
Change in dimension before mitral valve opening	23 (16)*†	16 (9)†	5 (4)
Minimum dimension to mitral valve opening (ms)	75 (45)†	70 (45)†	35 (20)
Peak rate of dimension increase (cm/s)	9·8 (3·8)†	9·7 (3·5)†	15·5 (4·8)
Peak rate of posterior wall thinning (cm/s)	5·9 (2·9)†	6·7 (3·3)†	9·8 (2·5)
LVEDP (mm Hg)	22 (11)	21 (8)	

LVEDD, left ventricular end diastolic dimension; LVEDP, left ventricular end diastolic pressure; *p < 0·05 *v* group with left ventricular hypertrophy; †p < 0·05 *v* controls.

ferences existed with respect to age. Left ventricular end diastolic dimension was greater in patients with ischaemic heart disease (5·9 (1·1) cm) than both those with left ventricular hypertrophy (4·8 (1·0)) and the controls (5·0 (0·6)). The RR interval was significantly shorter in both patient groups compared with controls (800 (200) ms and 835 (140) *v* 930 (155)). These differences did not affect within group analysis.

The mean value for peak E wave velocity was greater in patients with left ventricular hypertrophy than in both other groups (0·86 (0·31) *v* 0·71 (0·20) and 0·69 (0·17) m/s), in whom the mean value did not differ significantly. The mean value for peak A wave velocity was also greater in patients with left ventricular hypertrophy than in the controls (0·68 (0·3) *v* 0·54 (0·12) m/s) so that the A/E ratio did not differ significantly (0·87 (0·49) *v* 0·79 (0·28)), although the SD was clearly higher, reflecting the wide range of values for the A/E ratio seen in left ventricular hypertrophy. Although the A wave velocity was less in patients with ischaemic heart disease than normal (0·43 (0·29) m/s), once again the mean A/E ratio did not differ significantly from normal (0·72 (0·60)), the high SD similarly reflects the wide range of values seen in ischaemic heart disease. The mean value for E wave acceleration in the group with left ventricular hypertrophy was not significantly lower than the other two groups.

Table 2 Subgroup analysis of the group with ischaemic disease (mean (SD))

	Dilated cavity (LVEDD > 6 cm)	*Non-dilated cavity (LVEDD < 6 cm)*
Age (y)	56 (9)*	62 (9)†
LVEDD (cm)	6·8 (0·5)	5·0 (0·8)
Shortening fraction (%)	14·6 (4·5)*	23·1 (7·1)
RR Interval (ms)	765 (200)†	840 (195)
A wave velocity (m/s)	0 39 (0·31)†	0·47 (0·29)
E wave velocity (m/s)	0·74 (0·17)	0·66 (0 22)
A/E ratio	0·57 (0·52)	0·86 (0·65)
Isovolumic relaxation time (ms)	55 (30)	70 (35)
Change in dimension before mitral valve opening (%)	21 (14)†	25 (18)†
Minimum dimension to mitral valve opening (ms)	70 (40)†	80 (45)†
Peak rate of dimension increase (cm/s)	9·2 (3·1)†	10·4 (4·3)†
Peak rate of posterior wall thinning (cm/s)	5·5 (2·8)†	6·2 (3)†
LVEDP (mm Hg)	22 (9)	20 (12)

LVEDD, left ventricular end diastolic dimension; LVEDP, left ventricular end diastolic pressure; *p < 0·05 *v* group with normal cavity dimension; †p < 0·05 *v* normal control group.

The mean values of isovolumic relaxation time seen in each group were identical (60 (35), 60 (25), 60 (10) ms), although the range of values seen in both patient groups was much wider than in the controls. The time from aortic closure to the start of flow was significantly longer than the isovolumic relaxation time measured as aortic closure to the point of mitral cusp separation in all groups. This discrepancy was 25 ms in left ventricular hypertrophy and normal people, and 45 ms in those with ischaemic heart disease. This discrepancy did not significantly differ between those ischaemic patients with and without incoordinate relaxation. In both ischaemia and hypertrophy, measures of incoordination during isovolumic relaxation were greater than in the controls, both as the percentage change in dimension before mitral valve opening, and the time interval from minimum cavity dimensions to mitral valve opening. These two measures were, as expected, highly correlated.

Peak rates of dimension increase and posterior wall thinning were significantly reduced in both patient groups compared with controls.

WITHIN GROUP COMPARISON

Cavity size

To investigate the effect of cavity dilatation, we divided patients with ischaemic heart disease into two groups according to the end diastolic dimension. Those with left ventricular dilatation were younger and with a significantly reduced shortening fraction, but there were no other significant differences between the two groups in terms of Doppler or M mode indices of diastolic function. Indices of diastolic function in both subgroups were significantly different from normal (table 2).

Isovolumic relaxation

Figure 1 shows that the isovolumic relaxation time and the Doppler A/E ratio for all patients with left ventricular disease were linearly related. When subdivided into two groups depending on isovolumic relaxation time, those with shorter values had significantly less incoordination and a greater peak rate of dimension increase. Importantly however, *both* subgroups had M mode indices of diastolic function that were significantly different from normal (table 3).

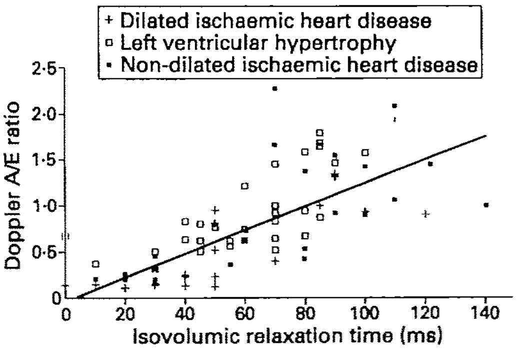

Figure 1 Relation between Doppler A/E ratio and isovolumic relaxation time for all three patient groups. The three regression lines were so similar that they are represented by a single line.

Table 3 Subgroup analysis of all patients with left ventricular disease, based upon isovolumic relaxation time (mean (SD))

Variable	*IVRT < 60 ms*	*IVRT > 60 ms*
Isovolumic relaxation time (ms)	40 (15)	90 (20)
Change in dimension before mitral valve opening (%)	15 (11)*†	27 (15)*
Minimum dimension to mitral valve opening (ms)	55 (35)*†	90 (40)*
Peak rate of dimension increase (cm/s)	10·8 (3·6)*†	8·7 (3·5)*
Peak rate of posterior wall thinning (cm/s)	6·8 (3·3)*	5·7 (2·8)*
LVEDP (mm Hg)	23 (9)	19 (9)

IVRT, isovolumic relaxation time; LVEDP, left ventricular end diastolic pressure; *p < 0·05 *v* normal control subjects; †p < 0·05 *v* group with IVRT > 60 ms.

Effect of age on filling pattern

A/E correlated with age in normal individuals ($r = 0{\cdot}74$), to a lesser extent in those with left ventricular hypertrophy ($r = 0{\cdot}41$), but not significantly in those with ischaemic heart disease (table 4).

SEPARATE EFFECTS OF ISOVOLUMIC RELAXATION TIME AND INCOORDINATION UPON FILLING PATTERN

In left ventricular hypertrophy and those ischaemic patients without left ventricular dilatation, A/E was correlated both with isovolumic relaxation time ($r = 0{\cdot}68$ and 0·60 respectively), and with incoordinate relaxation (measured as a percentage change before mitral valve opening, $r = 0{\cdot}65$ and 0·61, table 4). In those ischaemic patients with left ventricular dilatation (end diastolic dimension >6 cm), the influence of incoordination was lost and isovolumic relaxation time became the dominant influence upon A/E ($r = 0{\cdot}82$). This was despite considerable incoordinate relaxation being evident in this subgroup. Stepwise regression confirmed that weak correlations of end diastolic pressure and RR interval with A/E became insignificant once isovolumic relaxation time had been taken into account. Multiple regression analysis for the group with ischaemic heart disease, and that with left ventricular hypertrophy, showed that isovolumic relaxation time (IVRT) and incoordinate relaxation account for over 50% of the variance in the Doppler A/E ratio.

In patients with ischaemic heart diseases, the regression equation was:

$$A/E = -0{\cdot}128 + 0{\cdot}011\ \text{IVRT} + 0{\cdot}009\%\ \text{change before mitral valve opening;}$$

$$R^2 = 52\%$$

In left ventricular hypertrophy, it was:

$$A/E = -0{\cdot}095 + 0{\cdot}011\ \text{IVRT} + 0{\cdot}017\%\ \text{change before mitral valve opening;}$$

$$R^2 = 60\%$$

Table 4 Correlation coefficients of the A/E ratio

	Controls	*Left ventricular hypertrophy*	*Ischaemic heart disease non-dilated*	*Ischaemic heart disease dilated*
Age	0 74**	0·41*	0·28	0·23
Isovolumic relaxation time	0 04	0·68**	0·60**	0·82**
Incoordinate relaxation:				
Change in dimension before mitral valve opening (%)	0·25	0·65**	0·61**	0·27
Minimum dimension to mitral valve opening (ms)	0·15	0·72**	0·50**	0·22
RR Interval	0·02	0·17	0·09	0·54**
LVEDP		−0·37*	−0:48*	−0·2

LVEDP, left ventricular end diastolic pressure; *p < 0·05; **p < 0·01.

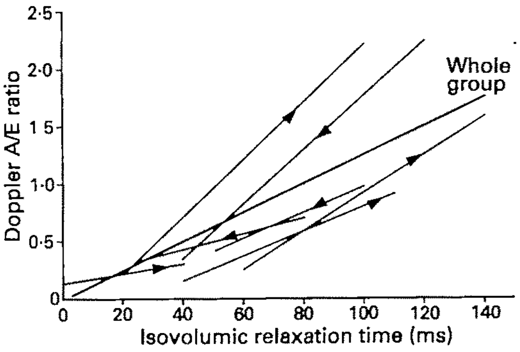

Figure 2 Results of changes in the Doppler A/E ratio and isovolumic relaxation time in the seven patients studied on two occasions, with the largest changes. The arrows indicate the direction of change and the broad line represents the regression line derived from the group as a whole from fig 1. Note that changes within individual patients behave in a similar fashion to differences between patients.

EFFECT OF ISOVOLUMIC RELAXATION TIME UPON ACCELERATION

Isovolumic relaxation time correlated significantly with acceleration of early diastolic flow in both ischaemic heart disease ($r = -0{\cdot}74$, $p < 0{\cdot}01$), and left ventricular hypertrophy ($r = -0{\cdot}71$, $p < 0{\cdot}01$).

CHANGES WITHIN PATIENTS

Sixteen patients were studied more than once, and in all cases, changes in the duration of isovolumic relaxation time were matched by a concomitant change in the Doppler A/E ratio. The time between the two studies was 6 (5) months. Figure 2 shows the findings in the seven patients with the greatest changes. Some patients had increased isovolumic relaxation time and Doppler A/E ratio, and conversely, those whose isovolumic relaxation time got shorter had a reduced A/E ratio. Figure 3 shows the relation between the magnitude of change in isovolumic relaxation time and the magnitude of change in the A/E ratio for all patients. These striking changes occurred without any evidence that the underlying diastolic properties of the left ventricle had changed (table 5).

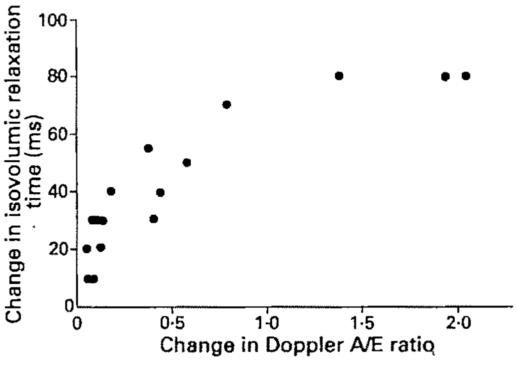

Figure 3 Relation between the size of change in the Doppler A/E ratio, plotted against the size of change in isovolumic relaxation time, in the 16 patients studied on two occasions.

Table 5 Doppler A/E ratio, isovolumic relaxation time, and indices of diastolic function in 16 patients studied on two occasions: data are presented for the lower A/E ratio and higher A/E ratio studies (mean (SD))

	Value when A/E ratio was low	*Value when A/E ratio was high*
A/E ratio	0·46 (0·53)	1·01 (0·53)
Isovolumic relaxation time (ms)	40 (35)*	80 (40)
Peak rate of dimension increase (cm/s)	10·6 (3·4)	9·7 (4·1)
Peak rate of posterior wall thinning (cm/s)	8·8 (2·3)	7·6 (3·6)

*$p < 0.05$ *v* group with higher A/E ratio.

Discussion

The pattern of blood flow across the mitral valve during diastole is not determined by the presence or absence of left ventricular disease, but by simple newtonian mechanics. Acceleration or deceleration of blood is directly proportional to the applied force. A force is measured in fluid as a pressure gradient—that is, the rate of change of pressure with distance along the direction of flow. A complete description of the pressure gradients requires mapping of the three dimensional pressure field—the spatial distribution of pressure throughout the atrium, atrioventricular junction, and ventricle throughout the filling period. Such measurements are so complex that they have never been undertaken experimentally, let alone in intact patients with heart disease. Single determinants of left atrial or left ventricular pressure, particularly with respect to physiologically irrelevant reference points such as atmospheric or mid right atrial pressure, have given rise to confusing reports that attempt to relate filling pressures to Doppler measurements.[6,9,10] In the present study, therefore, we have explored other interrelations with Doppler measurements of the transmitral flow pattern, and shown the importance of two separate components of isovolumic relaxation in determining filling patterns.

There are an increasing number of publications relating isovolumic relaxation with early filling velocity, peak filling rate, or the A/E ratio in hypertrophic cardiomyopathy,[20] coronary artery disease,[21] left ventricular hypertrophy,[19] and dilated cardiomyopathy.[23] In the study on dilated cardiomyopathy, as in this study, A_2 to mitral cusp separation was used to measure isovolumic relaxation time. The discrepancy between this and the time interval of A_2 to the start of flow on Doppler has been shown to be 25 ms, on average, in controls and in left ventricular hypertrophy, and 50 ms in dilated cardiomyopathy.[24] We have now shown that in ischaemic heart disease as a whole, this discrepancy is 45 ms. Furthermore, we were unable to show any significant differences in this discrepancy between those ischaemic patients with and without incoordination, suggesting that the primary effect of the disturbance is to delay mitral valve opening itself, rather than the start of transmitral flow once the valve has opened. In the present study we were able to show an effect not simply on peak early diastolic flow velocity but on the peak initial acceleration of blood during early diastole. Further, the influence of isovolumic relaxation could be resolved by stepwise regression analysis, into two discrete components: isovolumic relaxation time itself and the extent of incoordination during isovolumic relaxation. Both were independently significant in patients with left ventricular hypertrophy or ischaemic heart disease with normal cavity size. We have already shown the importance of incoordination in affecting rapid filling during early diastole,[25] and the results of our patients with ischaemic heart disease and normal cavity size are entirely compatible with this study. In those ischaemic patients with cavity dilatation, however, isovolumic relaxation time was the only influence upon the A/E ratio. This was not due to a lack of incoordination in the patients with dilated ventricles; on the contrary, they had particularly incoordinate ventricles. This association between isovolumic relaxation and filling was very significant in all three patient groups with values of R^2 (and thus the proportion of overall variance of filling pattern accounted for) consistently above 50%. This implies that events before rather than after mitral opening, were the dominant determinants of both the initial acceleration of blood into the left ventricle, and of the A/E ratio of these patients with ventricular disease.

By definition a force is that which causes acceleration. In being so closely associated with initial acceleration, therefore, events during isovolumic relaxation must also be closely related to the forces causing blood flow from the left atrium to the ventricle—that is, to the atrioventricular pressure gradient. Several potential mechanisms exist to explain this connection. Isovolumic relaxation time itself has already been shown to be closely related to left ventricular filling pressure,[26] which may partly explain our findings. This simple relation, however, would not account for the additional effect of incoordination during isovolumic relaxation. Incoordinate wall motion is due to asynchronous termination of systole in different regions of the ventricle.[27] Clearly, this cannot be assessed in detail from the ventricular pressure pulse, but its overall effect is likely to slow the rate of fall of pressure, and thus to prolong isovolumic relaxation time independently of the pressure difference between the aorta and left atrium. Also, the early diastolic pressure drop across the mitral valve depends on the effective pressure within the left ventricle as well as the left atrium. Normally, left ventricular pressure in early diastole is negative to atmospheric pressure, reflecting the effect of restoring forces within the myocardium at end systole.[28-30] Dissipation of these forces by incoordinate relaxation would thus increase effective ventricular pressure towards zero by the time the mitral valve opens and so reduce the atrioventricular pressure gradient independently of any change in orthodox estimates of left atrial pressure (made with respect to the atmosphere or mid right atrium). The absence of the effect of incoordination on early diastolic acceleration in patients with cavity dilatation, unlike its clear effect in the other two groups, can also be explained on this basis. We have already presented evidence suggesting that normal ventricular restoring forces are maintained in patients with left ventricular hypertrophy,[31] but not in those with cavity dilatation and low ejection fraction.[23] If restoring forces are not generated at end systole, then incoordinate wall motion during isovolumic relaxation would not be expected to have any further effect on early diastolic transmitral flow. These effects of incoordination are not easy to reproduce in any experimental model, and must thus be studied clinically.

The linear relation between the Doppler A/E ratio and isovolumic relaxation time has practical consequences. If isovolumic relaxation time is less than 60 ms, the A/E ratio will be normal ($<1{\cdot}0$) regardless of whether or not diastolic disease is present. We were able to show that such patients had reduced rates of dimension increase and posterior wall thinning, thus clearly dissociating filling pattern from diastolic disease. Further evidence for this dichotomy came from observations on the same patient under different circumstances when large changes in isovolumic relaxation time were accompanied by corresponding alterations in the A/E ratio, under conditions in which the fundamental diastolic properties of the ventricle are most unlikely to have altered. Indeed no significant changes were recorded in peak rates of dimension increase or peak rates of posterior wall thinning in these patients. It is clearly important to know this when interpreting the effects of interventions: small changes in the A/E ratio and isovolumic relaxation time have, for example, been taken as evidence of improved diastolic properties of the ventricle after angioplasty.[32] These changes might well be explained in terms of simple alterations in loading conditions.

Isovolumic relaxation time has been seen as little more than a brief period between the end of ejection and the start of filling. Its physiological significance, however, is far greater than this. The relative effects of the two distinct processes we have defined, differ between patient groups. The duration of isovolumic relaxation depends on loading conditions. Superimposed on this are the effects of incoordinate wall motion that not only reduce the rate of left ventricular pressure decline, but also interfere with the transmission of restoring forces from their generation at end systole to their coupling to filling at the time of mitral valve opening. It is thus unsatisfactory to consider these events as the single entity of "relaxation" and still more so to describe them as a time constant of left ventricular pressure fall. It is now apparent that pressure fall is not exponential, even in healthy individuals.[29 33] When the time of onset and rate of pressure decline both vary in different regions of the ventricle, then this assumption of exponential pressure fall is still more questionable. Also, measuring it is an invasive procedure whereas the simple approach we have outlined, based on M mode echocardiography and phonocardiography, is not only non-invasive, but allows both components to be determined independently.

The major diastolic function of the ventricle is to increase its volume. This process is frequently abnormal in disease, and it is important to identify and possibly treat the underlying factors. Our results clearly show that it is during isovolumic relaxation and not after mitral valve opening that the pattern of filling is determined, so that equally it is before mitral valve opening that factors governing this important process should be sought. These may be primary disturbances of isovolumic relaxation itself, or more commonly are the result of abnormal function even earlier in the cardiac cycle,[34 35] the right ventricle,[36] or even in activation.[37 38] This approach is proving more fruitful than use of filling patterns to predict later diastolic properties such as cavity compliance, myocardial stiffness, or end diastolic pressure.

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Analysis of left ventricular regional wall motion in normal neonates

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Abstract

***Objective*—To investigate neonatal circulatory change by quantitative analysis of left ventricular regional wall motion.**

***Design*—Random prospective study.**

***Setting*—Department of paediatrics in a teaching hospital.**

***Participants*—66 neonates born after a normal pregnancy, labour, and delivery.**

***Interventions*—Quantitative analysis of left ventricular regional wall motion was performed on cross sectional echocardiograms. M mode, cross sectional, and Doppler echocardiograms were obtained simultaneously.**

***Main outcome measures*—Manually traced endocardial contours at end diastole and at end systole were realigned by superimposing the centre of the ventricular mass and the axis. The contours were divided into 24 segments with 24 radii of equal arc from the centre. Then the ratio of the change in area between the outline of the contour and the two hemiaxes was calculated automatically.**

***Results*—There was hyperkinesis of the interventricular septum in the first 24 hours after birth which continued until the end of the first week. Simultaneous echocardiographic examination showed evidence of pulmonary hypertension, as indicated by an increase in the ratio of the right pre-ejection period to the right ventricular ejection time (RPEP/RVET) and of the diameter ratio of the pulmonary artery to the aorta and a shortening of the acceleration time of pulmonary arterial blood flow. These features disappeared within a week.**

***Conclusions*—Hyperkinesis of the interventricular septum may reflect circulatory changes that are characteristic of the early neonatal period.**

(*Br Heart J* 1992;68:574–9)

Immediately after birth the lungs take over gas exchange from the placenta and there are major circulatory changes. Pulmonary blood flow increases rapidly and the ductus arteriosus and the foramen ovale close functionally. The pulmonary and the systemic circulations operate in series rather than in parallel. Then the left and right ventricular outputs increase considerably and become equal. Both left ventricular preload and afterload increase because placental blood flow stops and the resistance of the systemic vascular bed is high. Pulmonary arterial blood pressure and vascular resistance fall progressively to the adult level within two to six weeks after birth. These changes were studied in lambs,[1-3] at neonatal catheterisation[4 5] and during echocardiographic examination.[6-13]

We noticed that cross sectional echocardiography showed transient hyperkinesis of the interventricular septum in the early neonatal period. This observation prompted a quantitative analysis of left ventricular regional wall motion and a comparison with M mode, cross sectional and Doppler echocardiographic findings.

Patients and methods

We performed M mode, cross sectional, and Doppler echocardiographic examinations on 66 neonates and infants. Each of them had had a normal gestation, labour, and delivery. Informed consent was obtained from their mothers according to a protocol approved by the Human Subjects Committee. They were divided into three groups according to their age. Group A was 22 neonates studied within 24 hours after birth; group B, 18 aged 4–7 days; and group C, 26 infants who were about a month old (table 1).

ECHOCARDIOGRAMS

The echocardiograms were obtained with a Toshiba SSH 60A with a 5·0 MHz transducer while the neonates were sleeping. The left ventricular images of the parasternal short axis view at the level of papillary muscles, the apical long axis view, and the apical four chamber view were recorded on the video tapes. The pulsed Doppler scanning frequency was 3·75 MHz. M mode and Doppler tracings were printed on hard copy.

ANALYSIS OF LEFT VENTRICULAR REGIONAL WALL MOTION

Regional wall motion was analysed with a Kontron Cardio 200 system. The endocardial borders at end diastole and at end systole were traced manually, with a light pen, and were realigned for translation and rotation by superimposing the centre of each contour and the axis according to the floating method. Then the contours were divided into 24 segments by 24 radii of equal arc from the centre and the ratio of change of each area between the outline of the endocardial margin and the two hemiaxes was calculated automatically according to the area method. The end diastolic and the end systolic frames were defined visually as the largest and the smallest left ventricular cavity

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Table 1 Data on noenates (mean (SD))

	Group A	*Group B*	*Group C*
n	22	18	26
Gestational age (week)	40·24 (1·53)	40·22 (1·53)	40·14 (1·38)
Body weight at birth (g)	3404 (390)	3304 (297)	3261 (389)
Age at study	10·14 (6·10)	5·89 (0·83)	30·92 (2·13) days
Body weight at study (g)	3404 (390)	3223 (283)	4424 (515)
Heart rate (beats/min)	120·9 (16·2)	125·1 (16·6)	140·5 (16·0)

areas, respectively. They coincided with the peak of the R wave and the end of the T wave on the electrocardiogram. The tracing was performed by one observer.

In the short axis view the endocardial borders were traced counter-clockwise from the posterior junction of the right ventricular free wall and the interventricular septum. The centre and the axis were defined as the centre of the mass and the radius drawn from the centre to the start of the tracing. Twenty four small segments were subdivided into six large segments anatomically and the mean ratio of area change was calculated for each large segment (fig 1A).

In the long axis view the contours were traced clockwise from the aortomitral junction. The centre was taken as the mid-point of the left ventricular long axis drawn from the aortomitral junction to the apex. This line was also defined as the axis. As these segments were excluded from the analysis the initial three segments included the mitral orifice. Another 21 segments were analysed and grouped into seven large segments (fig 1B).

In the four chamber view the endocardial contours were traced from the septal side of the mitral orifice. The long axis was drawn from the mid-point of mitral orifice to the apex and the mid-point of it was determined as the axis and the centre. The contours were grouped into six large segments (fig 1C).

M MODE, CROSS SECTIONAL, AND DOPPLER ECHOCARDIOGRAPHY

Simultaneous M mode, cross sectional, and Doppler echocardiographic examinations were performed. Right and left ventricular systolic time intervals, the pre-ejection period (PEP), and ejection time (ET) were measured on the hard copies of M mode echocardiograms, and the PEP/ET ratio was calculated.

The diameters of the pulmonary artery and the aorta were measured on the parasternal short and long axis views of the cross sectional echocardiograms, and their ratio was calculated. On the short axis view, left ventricular diameter ratio (that is, the ratio of the anterior-posterior wall diameter to the septal-lateral wall diameter) was calculated at the end diastole and at the end systole to assess left ventricular distortion.

Maximal flow velocities and acceleration times (duration from the onset of ejection to the point at peak flow velocity) were measured by pulsed Doppler echocardiography from Doppler velocity curves sampled above the pulmonary valve on the parasternal short axis view and above the aortic valve on the apical long axis view. The existence and the direction of shunt flows through the ductus arteriosus and the foramen ovale were evaluated with a sampling volume in the main pulmonary artery on the parasternal short axis view and at the left side of the patent foramen ovale on the subxiphoid four chamber view.

STATISTICAL ANALYSIS

Group data were compared by an analysis of variance. A p value less than 0·05 was regarded as statistically significant. All data were expressed as mean (SD).

Results

REGIONAL WALL MOTION OF THE LEFT VENTRICLE

For the first 24 hours after birth the left ventricle was distorted at end systole because the interventricular septum was flattened though the left ventricle was almost circular at end diastole. The interventricular septum was hyperkinetic at this time. One month after birth, however, left ventricular wall motion was like that in adults (fig 2). Hyperkinesis of the interventricular septum showed itself as an increase in the ratio of area change in the septal region in all three views.

In the short axis view the ratio of area change at the mid-septal segment in groups A and B

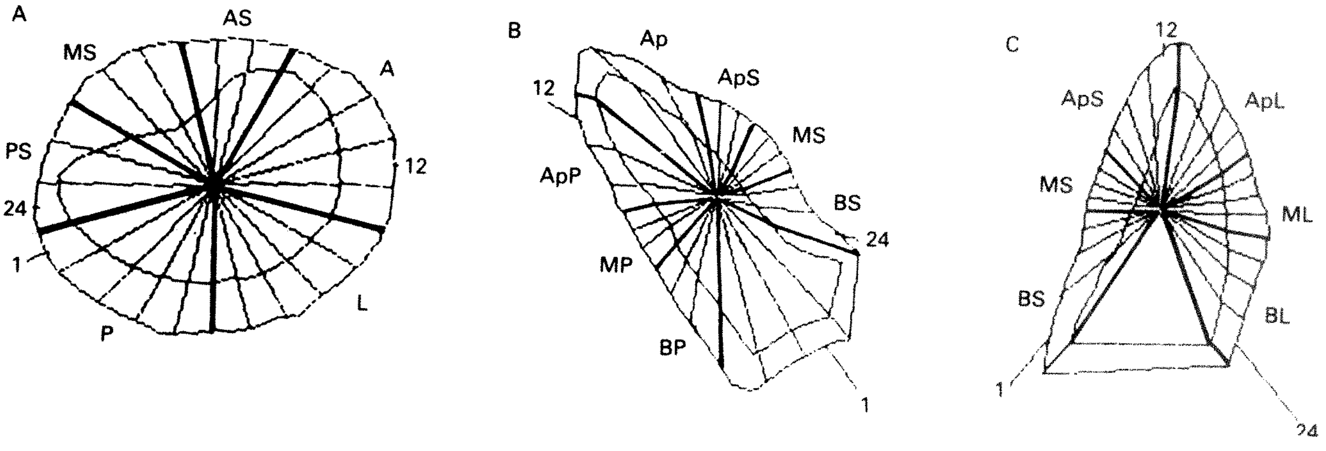


Figure 1 Segmentation scheme in the parasternal short axis view (A), in the apical long axis view (B), and in the apical four chamber view (C). P, posterior; L, lateral; A, anterior; AS, anteroseptal; MS, midseptal; PS, posteroseptal; BP, basal posterior; MP, midposterior; ApP, apical posterior; Ap, apical; Aps, apical septal; BS, basal septal; ApL, apical lateral; ML, midlateral; BL, basal lateral.

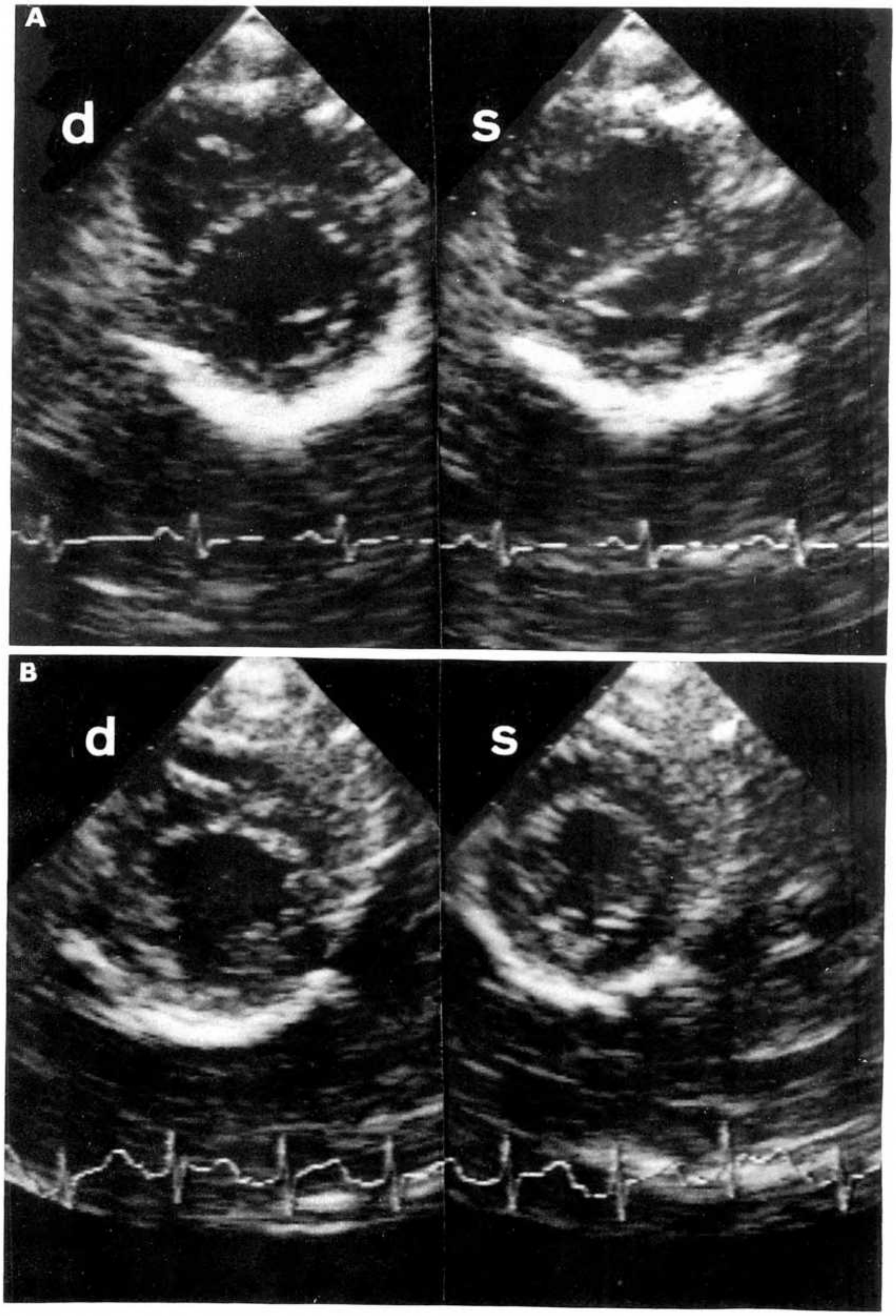


Figure 2 Neonatal left ventricular wall motion in the short axis view 14 hours after birth (A) and a month after birth (B). d, end diastole; s, end systole.

(66·4 (8·4)% and 54·6 (7·6)%) was significantly greater than in group C (46·8 (6·3)%). In group C the ratios for area change were almost equal over all segments, reflecting the circular configurations at end diastole and at end systole (fig 3A).

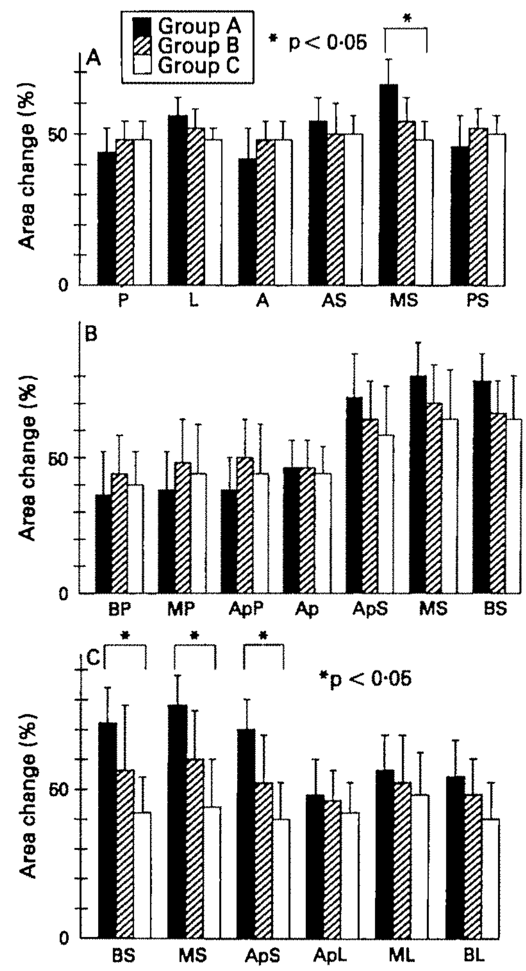
In the long axis view septal wall motion tended to increase in all groups. But there was no significant change with the age of the group (fig 3B).

In the four chamber view, ratios of area change of all septal segments were significantly higher in groups A and B than in group C. The ratios in groups A, B, and C were respectively 72·1 (12·7)%, 55·4 (21·3)%, and 42·1 (11·7)% in the basal septal segment; 78·9 (10·3)%, 59·7 (15·7)%, and 43·4 (15·4)% in the mid-septal segment; and 70·1 (10·7)%, 51·3 (15·5)%, and 40·1 (11·4)% in the apical septal segment (fig 3C). In group C the ratios for area change were similar in all regions.

CROSS SECTIONAL, M MODE, AND DOPPLER ECHOCARDIOGRAPHY (TABLE 2)

Simultaneous cross sectional echocardiographic examinations showed an increase of the

Figure 3 Changes of left ventricular regional wall motion in the parasternal short axis view (A), in the apical long axis view (B) and in the apical four chamber view (C). There was significant decrease in ratio of area change at the mid-septal (MS) region in the short axis view, and at the basal septal (BS), the mid-septal (MS), and the apical septal (ApS) region in the four chamber view ($p < 0{\cdot}05$ by analysis of variance).



ratio of the diameter of the pulmonary artery to the diameter of the aorta in group A compared with groups B and C. The left ventricular diameter ratio at end systole gradually decreased towards one, whereas at end diastole the ratio was already nearly one within 24 hours after birth.

M mode echocardiographic examinations showed that LPEP/LVET in groups A and B was higher than in group C. RPEP/RVET was also higher in group A than in group B or C.

Maximal velocities in the aorta and in the pulmonary artery, determined by pulsed Doppler echocardiographic examinations, increased steadily with the age of the group. The acceleration time in the pulmonary artery was significantly shorter in group A than in group B. Ductal shunt flow was detected as diastolic or continuous forward flow, suggesting a bi-directional or a left-to-right shunt, in the main pulmonary artery in 12 (57%) of 21 neonates in group A. It was not detected in groups B or C. Left-to-right shunt flow from early systole to late diastole was seen at the foramen ovale in group A (81%) accompanied by fluttering of the atrial septum. It was also common in groups B and C, but sometimes it was detected only during inspiration.

Discussion

The major circulatory changes after birth have been studied by various methods.[1-13] Because we noticed that cross sectional echocardiography showed hyperkinesis of the interventricular septum in neonates we attempted to measure changes in left ventricular regional wall motion and compare them with other circulatory indices in the first day, week, and month of life.

ANALYSIS OF LEFT VENTRICULAR REGIONAL WALL MOTION

Cross sectional echocardiographic techniques for regional wall motion analysis have been used to evaluate abnormalities of left ventricular contraction in adults with coronary artery disease[14-16] and to a more limited extent in children.[18-20] We thought that because of the clarity of the endocardial borders on the screen the method might be more useful in neonates than in adults. But because the heart beat and respiration produce considerable motion of the thorax in neonates we used the floating method rather than the fixed method that is used in adults.

In the short axis view we used the centre of the ventricular mass as the point of superimposition for endocardial contours. In the long axis view and the four chamber view we used the mid-point of the left ventricular long axis as the centre.[17] Analysis of regional wall motion by these methods showed that during the first week of life the interventricular septum was hyperkinetic. These findings accorded with the visual assessment of the cross sectional echocardiogram. They may have resulted from flattening of the interventricular septum at end systole and from bulging of the interventricular septum toward the right ventricle at end diastole. The hyperkinesis had disappeared by the end of the first month in the short axis and four chamber views. But it was still visible in the long axis view. More consistent results might have been obtained if the left ventricular long

Table 2 Echocardiographic data (mean (SD))

	AOD (mm)	PAD (mm)	PAD/ AOD	AP/SL End systole	AP/SL End diastole	LPEP/ LVET	RPEP/ RVET	AO-FV (cm/s)	AO-AcT (ms)	PA-FV (cm/s)	PA-AcT (ms)	PDA flow (%)	PFO flow (%)
Group A	7·75 (0·85)	10·09 (0·94)	1·33 (0·21)	1·57 (0·20)	1·18 (0·10)	0·321 (0·060)	0·373 (0·111)	99·3 (14·8)	53 (14)	80·5 (13·5)	64 (15)	12/21 (57)	18/21 (81)
Group B	8·18 (0·81)	8·71 (0·92)	1·07 (0·14)	1·24 (0·21)	1·09 (0·15)	0·319 (0·060)	0·205 (0·061)	104·7 (14·5)	44 (5)	93·0 (14·1)	83 (14)	0/15 (0)	10/14 (71)
Group C	8·18 (0·81)	9·90 (1·34)	1·13 (0·20)	1·10 (0·13)	1·08 (0·11)	0·276 (0·050)	0·213 (0·053)	112·1 (15·9)	58 (26)	93·7 (13·6)	72 (16)	0/18 (0)	15/18 (83)
ANOVA	p<0·01	p<0·01	p<0·01	p<0·01	NS	p<0·05	p<0·01	p<0·05	NS	p<0·01	p<0·01		

AOD, aortic diameter; PAD, pulmonary artery diameter; AP/SL, left ventricular diameter ratio (anterior-posterior wall diameter to septal-lateral wall diameter); LPEP, left pre-ejection period; LVET, left ventricular ejection time; RPEP, right pre-ejection period; RVET, right ventricular ejection time; FV, flow velocity; AcT, acceleration time; PDA flow, left to right or bilateral shunt flow through the patent ductus arteriosus; PFO flow, left to right shunt flow through the patent foramen ovale; ANOVA, analysis of variance.

axis had been taken from the apex to the midpoint of the aortic valve.

The position and the shape of the interventricular septum depend on the pressure gradient between left and right ventricles. The radius of curvature of the interventricular septum increased with right ventricular pressure overload, which is most pronounced at end systole.[21,22] However, the morphological change of the septum may be more sensitive to the change in transseptal pressure gradient in diastole than in systole.[23]

In 1983 Azancot *et al* used Fourier analysis to sudy the changes in left ventricular shape in the fetal and neonatal period,[24] and in 1987, Rein *et al* reported computer analysis of left ventricular regional wall motion by cross sectional echocardiography in normal neonates.[20] Rein *et al's* methods and results in the short axis view were similar to ours when we used the centre of the ventricular mass as the index site for superimposition. Because Rein *et al* also used the centre in the two chamber view the hyperkinesis was not visible. The method we used in the long axis view may be better than theirs for regional wall motion analysis. In our study septal hyperkinesia was more obvious in the four chamber view. We also compared the changes in regional wall motion with the results of M mode, and Doppler echocardiographic examinations.

CROSS SECTIONAL, M MODE, AND DOPPLER ECHOCARDIOGRAPHIC FINDINGS

The increase in the ratio of pulmonary artery diameter to aortic diameter RPEP/RVET, and the shortening of the acceleration time of pulmonary blood flow were consistent with pulmonary hypertension.[25,26] These features resolved after 24 hours of life, unless pulmonary hypertension continued. On the other hand, the diameter ratio of the anterior-posterior wall to the septal-lateral wall of the left ventricle in the short axis view at the end systole was increased just after birth, reflecting an increase in right ventricular systolic pressure. This ratio gradually decreased during the first month. In contrast, the ratio at end diastole was about one immediately after birth. This finding indicates that diastolic pressure was higher in the left ventricle than in the right ventricle. This accords with the finding that just after birth shunt flow through the foramen ovale was generally left-to-right even in diastole. The Doppler flow pattern of transmitral flow is known to change after birth because of the postnatal increase in transmitral flow and decrease in left ventricular compliance.[11]

Both of the ventricular changes that we found after birth may be the consequences of right ventricular hypertrophy, an increase in right ventricular systolic pressure caused by any remaining pulmonary hypertension, immature left ventricular systolic function, and a rapid increase in left ventricular diastolic pressure caused by the increase of preload and afterload.

IMPORTANCE AND APPLICATION OF REGIONAL WALL MOTION ANALYSIS

Though some indices of pulmonary hypertension had already resolved within a week of life, hyperkinesis of the interventricular septum was still present a week after birth. These findings indicate that changes in ventricular pressure and function continue in the week after birth.

The septal hyperkinesis disappeared in the first month of life—after this it should be regarded as abnormal. Analysis of regional wall motion may be useful in patients with congenital heart diseases because the presence of septal hyperkinesis may indicate pulmonary hypertension or an increase in right ventricular pressure caused by obstruction of the right ventricular outflow tract. Such analysis may also be helpful in evaluating these patients before and after operation.

We think that analysis of regional wall motion is a useful method of identifying abnormal ventricular function in those neonates in whom cardiac or respiratory disease is suspected.

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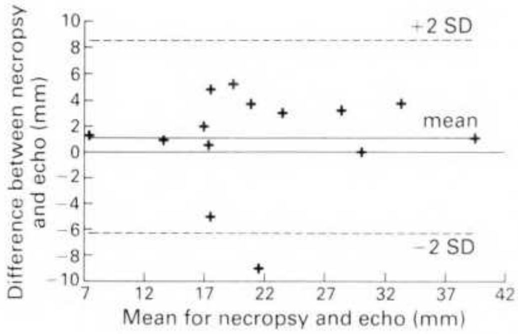

Figure 1 Differences between necropsy and echocardiographic measurements plotted against the mean for height of RA in the same fetus.[8] Only data from fetuses with less than eight weeks between the two measurements are included (n = 14, mean (SD) of the differences = 1·09 mm (3·70)).

ner and a medium focus 5 MHz transducer. For the purposes of this study, the videotapes of the echocardiograms were reviewed retrospectively and the findings were analysed with respect to displacement and dysplasia of the leaflets of the tricuspid valve, valvar stenosis or regurgitation as shown by Doppler studies, associated cardiac lesions, the cardiothoracic ratio, and the dimensions of the heart.

Right and left atrial heights were estimated from a typical four chamber section as the maximal distance during ventricular systole from the atrioventricular groove to the posterosuperior wall of the atrium. Ventricular dimensions were measured in diastole as the distance from the atrioventricular junction to the apex of the ventricle. The diameters of the atrioventricular junctions were taken as the maximal diastolic dimensions. The postmortem measurements were made from the heart and lungs fixed in formalin after they had been separated and weighed. The thicknesses of the free walls of the right and left ventricles were measured in their inflow components. All hearts were then sectioned to simulate the echocardiographic four chamber planes and measurements were performed as already described.

The echocardiographic and pathological measurements were then compared with the normal values for similar duration of gestation.[4-6] As an anatomical correlation to the cardiothoracic ratio obtained echocardiographically, the ratio of the weight of the heart was taken against the combined weight of the heart and lung and related to normal values.[7]

To assess the agreement between echocardiographic and postmortem measurements, we plotted the difference between the methods against their mean as described by Bland and Altman.[8] For the right atrium this is shown in a graph (fig 1), but for all the other measurements the mean difference was listed in the table.

Results

CORRELATIONS BETWEEN ECHOCARDIOGRAPHY AND MORPHOLOGY

During fetal life, Ebstein's malformation had been diagnosed in seven fetuses (fig 2A) and tricuspid dysplasia in 12 cases (fig 3A). At postmortem examination, these results were confirmed in six (fig 2B) and eight (fig 3B) cases respectively. One single false positive diagnosis of Ebstein's malformation was made in a fetus at 19 weeks gestation, in which necropsy showed gross dysplasia of the leaflets of the tricuspid valve without displacement. Isolated tricuspid valvar dysplasia was predicted in three fetuses, in which the leaflets of the tricuspid valve were, indeed, severely malformed and would have been the major cause of tricuspid incompetence. There was, however, a minimal displacement of about 5 mm of the mural and the septal leaflets in two, and major displacement of the mural leaflet with linear distal attachment of the anterosuperior leaflet in the other (fig 4A). The pathological diagnosis of each case, therefore, was Ebstein's malformation together with valvar dysplasia. The fourth

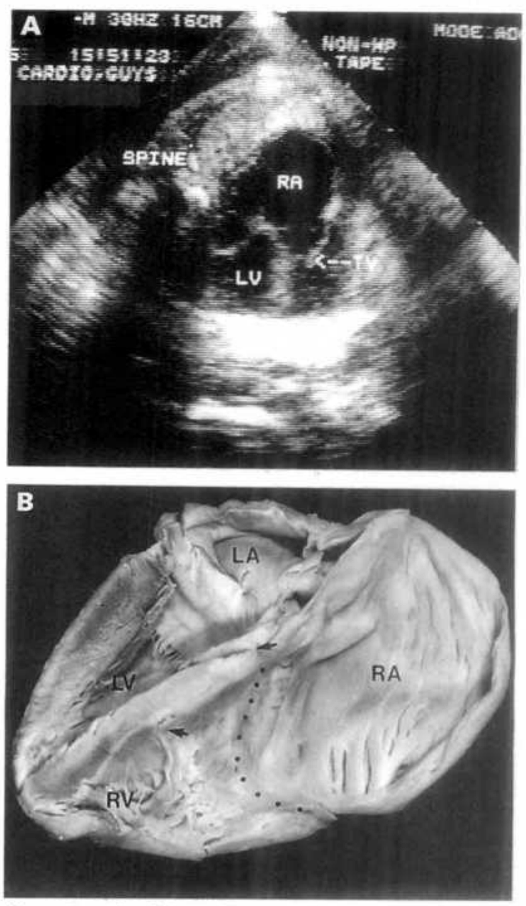

Figure 2 (A) Echocardiographic view in four chamber plane shows Ebstein's malformation in a 37 week old fetus. RA is grossly dilated and the hinge point of septal leaflet of the TV arises well down (arrow) the ventricular septum. (B) Pathological specimen of the same fetus has been photographed and printed in reverse so as to replicate the echocardiographic orientation. It confirms the noticeable displacement of the septal leaflet of the TV (arrows), which arises some distance from the atrioventricular junction (dotted line). LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve.

Mean (SD) measurements made echocardiographically and at necropsy and their mean difference

	n	*Echo*	*n*	*Specimen*	*n*	*Difference*	*n*	*Eight week difference*
RA (mm)	18	21·6 (8·9)	18	23·7 (11·6)	18	2·97 (8·0)	14	1·09 (3·7)
LA (mm)	17	12·5 (4·2)	19	14·8 (4·9)	17	2·66 (4·4)	13	1·51 (3·7)
RV (mm)	18	17·3 (6·4)	18	21·1 (7·3)	18	4·28 (4·4)	14	3·95 (4·5)
LV (mm)	18	17·4 (6·6)	19	21·7 (7·6)	18	4·74 (4·9)	14	2·90 (3·7)
TV (mm)	18	12·1 (5·2)	18	13·0 (5·9)	17	0·95 (4·8)	13	0·17 (4·2)
MV (mm)	18	9·4 (4·7)	18	8·3 (3·2)	17	−1·13 (3·3)	13	−1·19 (3·1)
PA (mm)	18	3·87 (2·0)	19	5·26 (3·0)	18	1·6 (2·1)	14	0·7 (2·3)
AO (mm)	18	5·72 (1·9)	19	6·23 (2·8)	18	0·63 (2·5)	14	0·02 (1·1)
PA/AO	18	0·68 (0·19)	19	0·84 (0·33)	18	0·22 (0·19)	14	0·19 (0·18)
CTR	19	0·68 (0·11)	19	0·44 (0·11)				

Eight week difference is the mean difference in which only fetuses with an interval of less than eight weeks are included. n, number of cases; RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; TV, tricuspid valve; MV, mitral valve; PA, pulmonary artery; AO, aorta; CTR, cardiothoracic ratio.

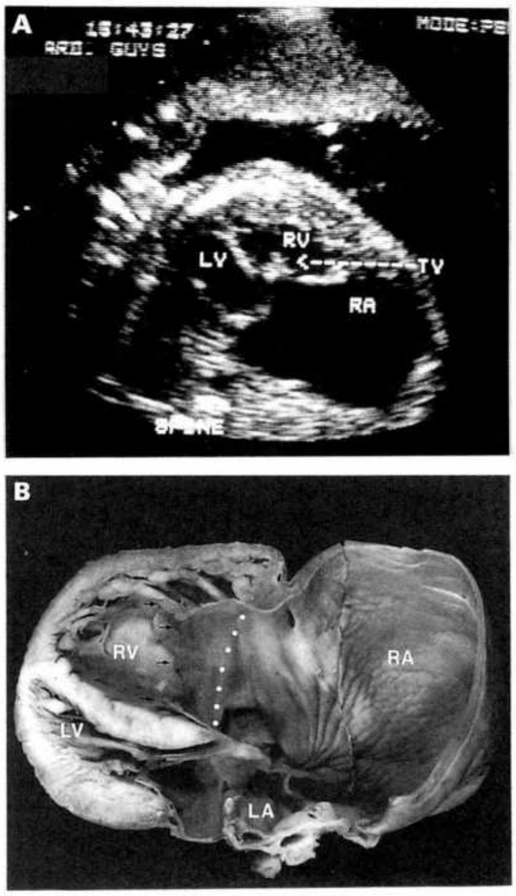

Figure 3 (A) Echocardiographic view in four chamber plane shows a dysplastic TV but with normal junctional attachments of the leaflets. (B) The four chamber view of the heart of the same fetus confirms the gross dilatation of the RA and shows the normal junctional attachments of the TV and mitral valves with offsetting at the septum: there is gross nodular dysplasia of the mural and septal leaflets (arrows).

case, in which Ebstein's malformation had not been found echocardiographically, showed displacement of the septal and mural leaflets, but with a most unusual dual formation of both leaflets (fig 4B). Some degree of tricuspid valvar dysplasia was appreciable echocardiographically in most cases irrespective of the diagnosis, and corresponded well with the extent of dysplasia estimated by gross examination of the necropsied specimens.[3] Among the cases with Ebstein's malformation in which downward displacement of the leaflets had been documented, it was not possible, in three cases, to diagnose echocardiographically the absence of the septal or the mural leaflet. Furthermore, the nature of the distal attachments of the tension apparatus (linear, (fig 4A), hyphenated, or focal) was not reliably classified by fetal echocardiography. Doppler echocardiography during fetal life showed signs of tricuspid regurgitation in all but one fetus, and no case showed evidence of stenosis.

In terms of associated malformations; the presence of one ventricular septal defect had been correctly predicted by fetal echocardiography; one additional small ventricular septal defect had been seen in one fetus when studied at the age of 20 weeks, but could not be located when the specimen was obtained at 24 weeks.

Prediction of atrial septal defects during fetal life is complicated by the patency of the oval foramen and such lesions were not recorded echocardiographically in this study. On postmortem examination, however, six atrial septal defects were found in each group. The atrioventricular and ventriculoarterial connections were discordant in two hearts with Ebstein's malformation (congenitally corrected transposition (fig 5)). These diagnoses had been made correctly during fetal life.

Eight cases of pulmonary atresia, and one case of pulmonary stenosis, were correctly predicted echocardiographically. No obstruction within the right ventricular outflow tract was found on postmortem examination in another two cases, one in which pulmonary atresia and the other in which pulmonary stenosis had been diagnosed prenatally. Two additional instances of pulmonary stenosis were found on postmortem examination. Some degree of mitral valvar dysplasia was encountered at necropsy in four hearts, three of which also had tricuspid dysplasia, which was not seen at echocardiographic examination in two fetuses. An example of divided right atrium (cor triatriatum dexter) was found in one case at necropsy.[3]

CORRELATIONS OF ECHOCARDIOGRAPHIC AND NECROPSY MEASUREMENTS

The results of the echocardiographic and necropsy measurements are expressed as the mean (SD) and the comparison between the two measurements is given by the mean difference according to Bland and Altman (table).[8]

Compared with the left atrium, the right was dilated in all hearts (except the two hearts with discordant atrioventricular connections, in

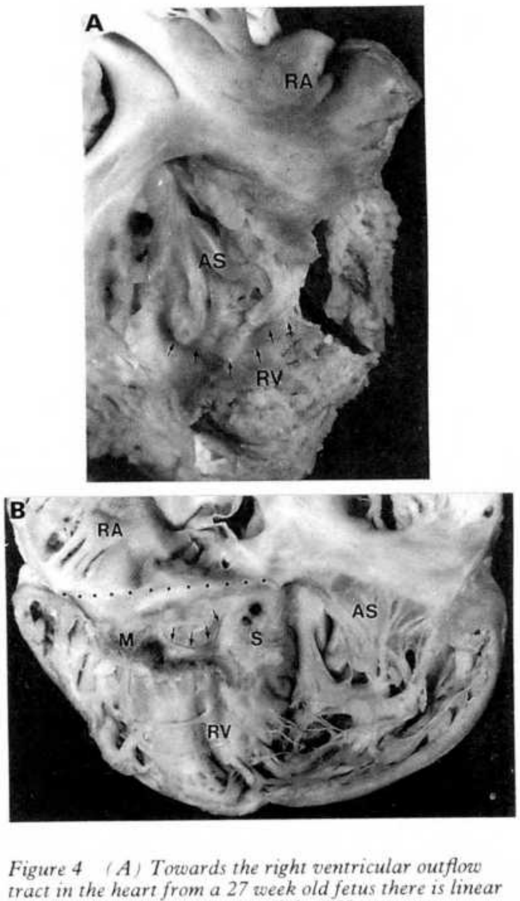

Figure 4 (A) Towards the right ventricular outflow tract in the heart from a 27 week old fetus there is linear attachment of the AS leaflet of the TV (arrows). (B) The right atrium and ventricle of another heart are opened to show downward displacement and dual formation of the M and S leaflets of the TV. AS, anterosuperior leaflet; M, mural; S, septal.

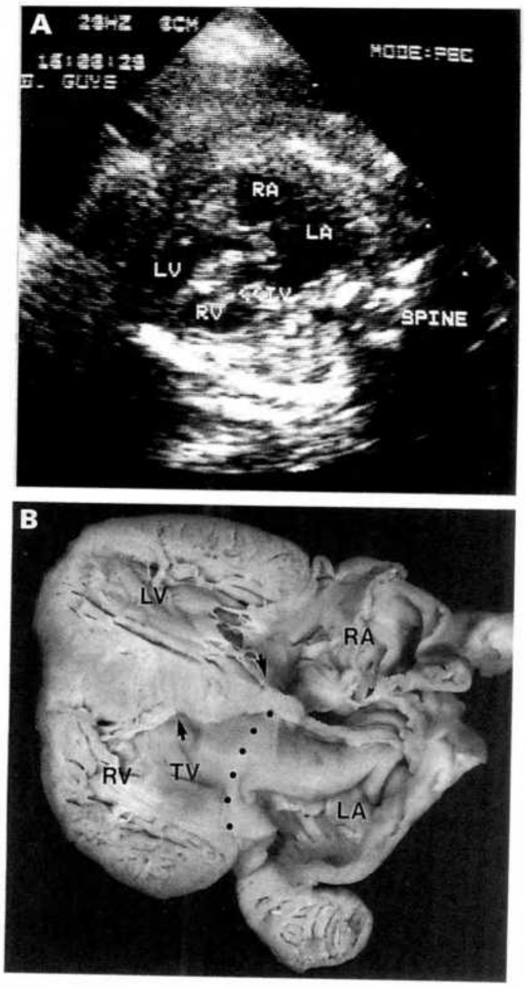

Figure 5 (A) These corresponding four chamber views of the heart with congenitally corrected transposition seen during fetal life and (B) on postmortem examination show gross downward displacement of the hinge points of the S and M leaflets of the TV away from the atrioventricular junction (arrows). Note the dilatation of the left atrium.

which the left atrium was larger). Echocardiographically, the mean height of the right atrium (or left atrium with discordant connections) was 21·6 mm whereas that of the left (or right atrium with discordant connections) was 12·5 mm. The corresponding values measured in the necropsied specimens were 23·7 and 14·8 mm. The mean (SD) difference of the two measurements for the height of the right atrium was 2·97 (0·8) mm. If the fetuses with an interval between the two measurements >eight weeks were not included in the calculation, however, there was a good agreement between the two methods (values marked with an asterisk in the table and the text) for the right atrium (fig 1) as well as for most of the other dimensions.

There was a non-significant difference between the echocardiographic and necropsied length of the right and the left ventricles, shown by a mean difference of 4·28 (3·95*) mm for the right and 4·74 (2·90*) mm for the left ventricle.

The tricuspid valve was larger in diameter than the mitral valve (mean 12·1 *v* 9·4 mm) as determined by echocardiographic measurement as well as in the anatomical measurement (mean 13·0 *v* 8·3 mm). Good agreement was found between the two methods of measurement for the tricuspid as well as for the mitral valve (table). When compared with mean values of the normal fetus,[4] the echocardiographic measurement showed enlargement of both atrioventricular valves in all but two hearts. Good agreement between the two methods was also shown for the diameter of both great arteries with a mean difference of 1·6 (0·7*) for the pulmonary trunk and 0·63 (0·02*) for the aorta. The ratio of the diameter of the pulmonary and aortic roots was reduced in all fetal scans as it was at necropsy, but at a lower degree leading to a mean difference of 0·22 (0·19*). The values were below expected normal measurements in 15 of 19 fetuses.[5]

The cardiothoracic ratio as determined echocardiographically was increased in all but one fetus (mean: 0·68) when compared with values for the normal fetus.[6] The postmortem equivalent of the cardiothoracic ratio, obtained by calculating the ratio of the weight of the heart to the combined weight of heart and lungs, was also greatly increased, with a mean of 0·44 compared with a normal range of 0·25 to 0·30.[7] Noticeable reduction in the thickness of the wall of the inlet component of the right ventricle was found at necropsy in six hearts with Ebstein's malformation and in three with tricuspid dysplasia. None of the previous measurements showed any correlation with this mural thinning.

Apart from the diameter of the mitral valve, the measurements taken from the specimens exceeded the values obtained by echocardiography.

Discussion

Congenital malformations of the tricuspid valve are known to show a gradation of changes, ranging from Ebstein's malformation with downward displacement of the valvar leaflets in isolation, through combinations of displacement and dysplasia, to exclusive dysplasia of normally attached leaflets.[6] Irrespective of the combinations, our previous studies have shown that differentiation of dysplasia and displacement is possible in most cases, even in prenatal life.[2 3] Our present study, combined with our previous investigations,[2 3] shows that prenatal ultrasound in our hands is a reliable method of diagnosing the malformation of the tricuspid valve in their different variations and in assessing the sizes of chambers and vessels. Thus different combinations of malformations afflicting the tricuspid valve may be readily defined by means of fetal echocardiography even before the midpoint of gestation. Failure to differentiate the two lesions was, apart from one case, related to lack of recognition of minor degrees of valvar displacement in Ebstein's malformation, or to the presence of extremely rare malformations of the valve, such as dual formation of the leaflets. This is difficult to assess echocardiographically even in postnatal life. The most common haemodynamic abnormality in either Ebstein's malformation or tricuspid dysplasia is valvar regurgitation as caused by dysplasia or even absence of the leaflets.[10] Echocardiographic determination of the degree of dysplasia was usually correct, whereas detection of lack of the leaflets was not. This is not unexpected, as recognition of absence of leaflets is rare at present during postnatal life.[11] The haemodynamic consequence of these anomalies, none the less, can be shown with precision by Doppler echocardiography, which showed tricuspid regurgitation in all fetuses. The combination of atrioventricular valvar insufficiency and structural heart disease is important to recognise, as it is known to indicate a poor prognosis in fetal life, especially when this results in cardiac failure prenatally.[12]

Even in prenatal and neonatal hearts, the cardinal feature of displacement in Ebstein's malformation is always confined to the septal and mural leaflets.[3] The anterosuperior leaflet of the valve, attached normally at the atrioventricular junction, was noted to have linear attachments of the distal tension apparatus in three fetuses of each group.[3] Recognition of this feature is particularly important in postnatal life, as, when present, it may cause a degree of obstruction between the inlet and outlet portions of the right ventricle.[13] Such stenosis has been correlated with early death (by three months) in infants with Ebstein's malformation.[14] It is the subcostal coronal view that in postnatal life is the most reliable to show the anterosuperior leaflet. Similar views will be needed during fetal life if in future there is need to distinguish between focal and linear attachment of the anterosuperior leaflet. With respect to flow across the valve, Doppler techniques showed only regurgitation in most fetuses. Even recognising the known caveats of underestimation of the degree of obstruction, stenosis due to distal tethering was most unlikely in our cases as all leaflets were seen to be in motion and the atrioventricular junction was dilated.[13]

The association with other cardiac lesions is known to make the prognosis in Ebstein's malformation worse.[13] Because of the comparable haemodynamic consequences, this seems likely also to be the case with tricuspid dysplasia. When there was an associated malformation there was no discrepancy between prenatal and postmortem diagnoses of deficiencies of the ventricular septal structures or in the recognition of discordant atrioventricular and ventriculoarterial connections. A small ventricular septal defect was not found on the postmortem examination of one case in which it had been diagnosed echocardiographically. We presume that it had closed spontaneously during the subsequent intrauterine life.[1] Atrial septal defects are difficult to predict during fetal life because of the patency of the foramen ovale. Correlation of that feature with the postmortem specimens, therefore, was not attempted. Minor degrees of dysplasia of the leaflets of the mitral valve were noted in some hearts at necropsy, a feature known to accompany Ebstein's malformation when seen in postnatal life.[9 15] To our knowledge, these lesions have not previously been described in tricuspid valvar dysplasia. Perhaps not surprisingly, these minor abnormalities were not recognised during fetal echocardiography. As the degree of dysplasia was mild, we do not anticipate it to have had any haemodynamic implications. This fact also held true in one case with division of the right atrium due to persistence of the valves of the embryonic venous sinus. This feature had not been noted on cross sectional echocardiography. In haemodynamic terms, this lesion is simply an exaggeration of the anatomical arrangement usually found during fetal life and augments the right to left atrial shunt already present.

Severe obstruction at the level of the pulmonary valve was seen in two fifths of the hearts with Ebstein's malformation and in two thirds of those with valvar dysplasia. The higher incidence of obstructive lesions of the right ventricular outflow tracts has already been described in pure tricuspid dysplasia,[2 9] and may contribute to the poor overall outcome in this group.[9] Although it is extremely difficult to distinguish organic atresia from the situation where the leaflets of the pulmonary valve are held closed by the high pressure in the pulmonary arteries,[13] pulmonary atresia was correctly predicted by means of fetal echocardiography in nearly all cases. Even beyond functional atresia, recognition of pulmonary stenosis in itself may easily be a source of error at fetal scans. This is because sequential studies have shown that Doppler gradients across the pulmonary valve may increase during fetal life,[2] and that stenosis can progress to atresia.[16] It is important, therefore, to note that the severity of cardiac lesions can progress during fetal life, and that the anatomical and the haemodynamic situation can change between the time of fetal scanning and when specimens are studied postnatally.[1] Taking this into consideration, the fetal echocardiographic diagnosis of malformations of the tricuspid valve and of associated cardiac anomalies shows good agreement with the findings at necropsy. Some minor disagreements are probably unavoidable but are mainly of academic interest or have minimal effects on prognosis.[1]

In this series, we have also analysed cardiac dimensions as determined by ultrasound and compared them with the known normal values. We have further related them to predictors of outcome well established in children and adults with Ebstein's malformation, comparing them then with the measurements obtained at postmortem. The most important predictive feature is the size of the heart. The cardiothoracic ratio was increased above the normal range[14] in all fetuses in our series, irrespective of whether they showed Ebstein's malformation or tricuspid valvar dysplasia, and was caused predominantly by enlargement of the right atrium. It has been assumed that cardiomegaly causes secondary hypoplasia of the lungs in the fetus,[2 17] thus increasing the risk of death due to hypoxia. Postmortem analysis of the weights of the lungs and heart in this series has already shown that the weight of the hearts was unequivocally increased,[3] whereas the weights of the lungs were within the lower range of normal. Echocardiographic measurements reflected areas, whereas the postmortem values represented weights, so the two cannot be compared. Nevertheless, the ratio based upon weight, with a mean of 0·44, is greatly increased compared with the normal ratio of 0·25 to 0·30 for the appropriate fetal age.[7] Thus, both sets of measurements reflect the cardiomegaly and the relatively small size of the lungs, which are almost certainly responsible for their inadequate functional capacity after birth.[18]

Prenatal and postmortem investigations of dimensions of chambers and vessels showed good agreement if the time between the measurements was small. It is hardly surprising that echocardiographic measurements were smaller than those from necropsy, as there was a mean period of four weeks between the two sets of investigations.

Keeping this restriction in mind, gross right atrial dilatation, claimed to be an important risk factor for early death in fetuses and newborns with Ebstein's malformation,[12] was correctly predicted by fetal echocardiography. Left ventricular compression as a consequence of dilatation of the right ventricle, also defined as a morphological risk factor,[12] was not found in our series. This may be caused partly by the different sites at which measurements were made.

In most specimens, irrespective of the diagnosis, considerable reduction was noted at necropsy in the thickness of the right ventricular wall, a feature not measured during the prenatal studies. As this finding is also recognised as a sign of poor clinical outcome in Ebstein's malformation,[12] it may be worth including in future fetal echocardiographic examinations.

Comparing fetal echocardiography with the postmortem morphological evaluation, therefore showed good agreement in differentiating Ebstein's malformation from dysplasia of the leaflets of the tricuspid valve and in defining associated cardiac lesions. Future examinations might include measurements of the thicknesses of the ventricular walls and estimations by Doppler echocardiography of mitral valvar flow. These could also serve as prognostic determinants of abnormalities of the tricuspid valve.

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Myocardial disarray in Noonan syndrome

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Abstract

***Objective*—To characterise the histopathology of the left ventricular hypertrophy commonly associated with Noonan syndrome by assessing the extent of myocyte disarray and therefore to define one aspect of the relation between this disease and idiopathic hypertrophic cardiomyopathy.**

***Design*—Blinded histological analysis.**

***Setting*—Hospital medical school.**

***Patients*—Six hearts of children with the Noonan phenotype and isolated ventricular hypertrophy were compared with age and sex matched controls.**

***Methods*—Histological analysis was performed with an image analyser under light microscopy. Representative sections from the entire left ventricular free wall were examined. Results were expressed as the percentage of fields showing disarray related to the number of fields evaluated: 100 fields were examined for each patient.**

***Results*—In the patients with Noonan syndrome myocardial disarray was present in the ventricular septum in 24 (5·7)% (mean (SD)) of fields and in the free wall in 22·2 (6·8)%. In the controls disarray was present in the septum in 3·8 (2·3)% of fields and in the free wall in 2·4 (2·8)%. In both regions the extent of disarray was significantly greater in patients with Noonan syndrome ($p < 0·0005$; 95% confidence interval 14 to 26·3 for the septum: $p < 0·005$, 95% confidence interval 11·4 to 28·2 for the free wall).**

***Conclusions*—The ventricular hypertrophy associated with Noonan syndrome is histologically similar to hypertrophic cardiomyopathy but whether the two diseases are the expression of the same genetic defect remains to be determined.**

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Asymmetrical septal hypertrophy has been documented in 23% of patients with Noonan syndrome.[1] The clinical and prognostic significance of this finding, however, is uncertain. In particular the relation to classic hypertrophic cardiomyopathy has not been assessed. Histopathological similarity between the two conditions could have both genetic and clinical implications. To characterise the histopathology we examined the hearts from six patients with Noonan syndrome and left ventricular hypertrophy who died in low cardiac output (4) or were given transplants (2) and compared the results with those in age matched controls.

Patients and methods

Table 1 shows the patients' details. Echocardiography was performed in four sets of parents of the six patients with Noonan syndrome and was normal in all eight, though one of them showed the Noonan phenotype. The age and sex matched controls were selected from among children dying of non-cardiac causes.

METHODS

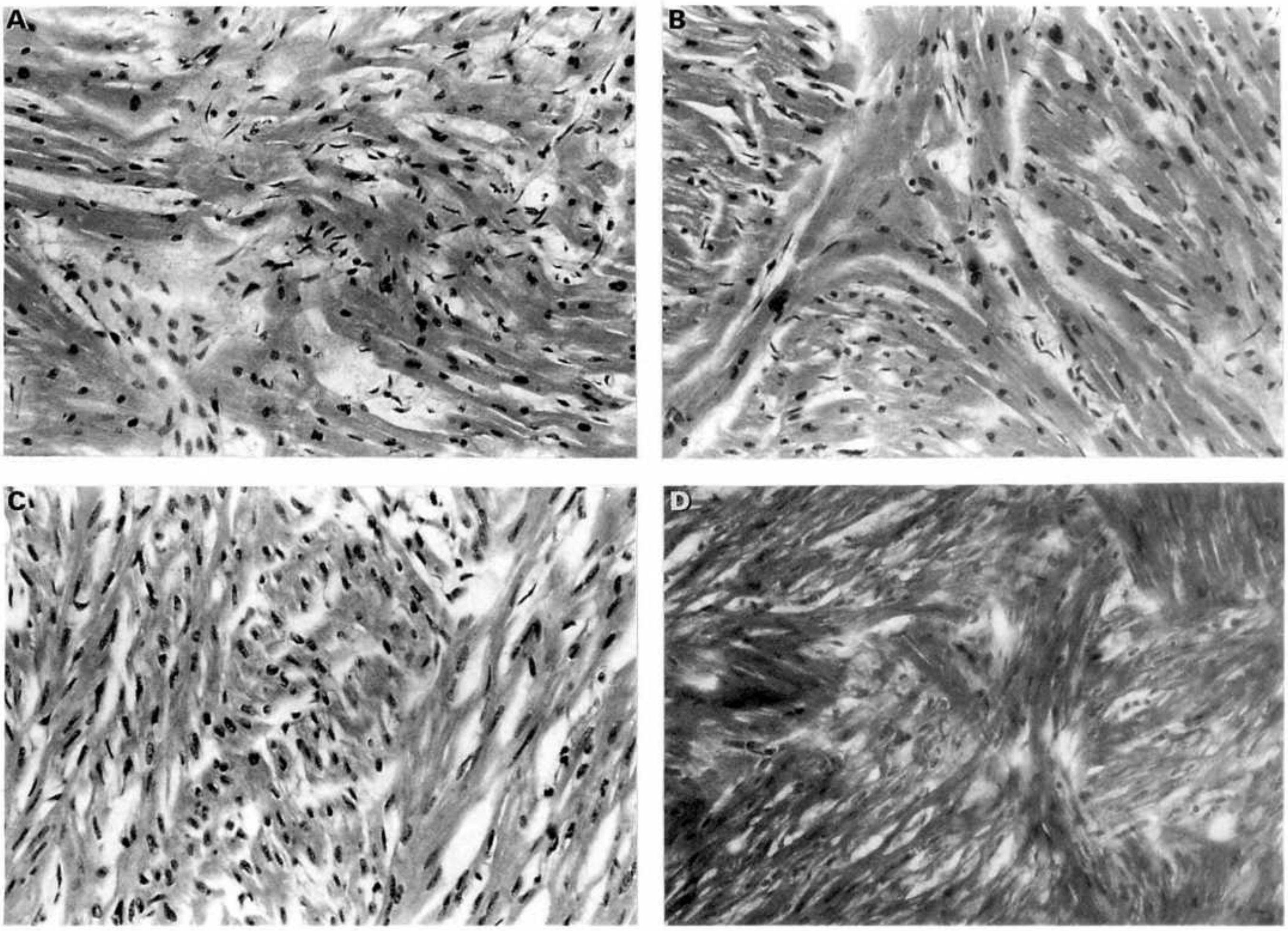
In all cases a transverse section of the ventricles was obtained, about one half the distance between the aortic valve and the left ventricular apex. Tissue specimens were fixed in formalin, embedded in paraffin, sectioned at a thickness of 6 μm and stained with haematoxylin and eosin. This permitted assessment of the ventricular septum and the left ventricular free wall in the same plane.

Myocardial disarray was evaluated with an image analyser (Optomax V, Analytical Measuring Systems, Cambridge, UK), under light microscopy at a magnification of × 16. The screen of the image analyser was regarded as a field, and the presence or absence of disarray was determined within that field. We classified cardiac muscle cell disorganisation according to the four different types that have been described in detail elsewhere.[2-4] In type IA the muscle cells were aligned perpendicularly or obliquely ("pinwheel"). Type IB consisted of relatively broad bundles of muscle that were orientated in an oblique or perpen-

Table 1 Patient details

Patient Number	*Sex*	*Symptoms*	*Death (D) or transplant (T)*	*Age at (D) or (T) (month)*	*Echo*
1	M	SOBE	T	120	Symm BVH
2	F	CCF	D	2	ASH
3	F	CCF	D	6	ASH
4	M	SOBE CCF	T	24	ASH
5	M	CCF	D	4	ASH
6	M	CCF	D	0·25	ASH

ASH, asymmetrical ventricular hypertrophy; CCF, congestive cardiac failure; Echo, cross sectional echocardiography; SOBE, shortness of breath on exertion; Symm BVH, symmetrical biventricular hypertrophy.



Types of disarray shown in Noonan syndrome. (A) type IA; (B) type IB; (C) type IIA; (D) type IIB.

dicular way. Type IIA disorganisation consisted of narrow longitudinal bundles between transversely cut cells. Type IIB was similar to IIA but the bundles of longitudinal muscles were more linear. Therefore type I disorganisation involved areas in which cardiac muscle cells were cut longitudinally and type II disorganisation involved both longitudinally and transversely cut cardiac muscle cells.

The ventricular septum was evaluated in all patients with Noonan syndrome, and 100 fields per section were counted for each patient. It was possible to evaluate the left ventricular free wall in only five of the six patients with Noonan syndrome (sections were not available in one patient). Both the ventricular septum and the free wall were evaluated in all six age matched controls: again 100 fields per section were analysed.

The extent of disarray was expressed as the percentage of total fields in which disarray was present. All patterns of myocyte disarray were included in the assessment. The severity of disarray in each field was not assessed—merely its presence or absence.

Table 2 Disarray in ventricular septum (total number of fields showing disarray in a 100 fields examined for each patient

Patient	*IA*	*IIA*	*IB*	*IIB*	*Total*
1	1 (1)	0 (0)	10 (2)	11 (0)	22 (3)
2	1 (0)	2 (0)	9 (0)	4 (0)	16 (0)
3	1 (1)	8 (0)	3 (4)	18 (0)	30 (5)
4	1 (1)	3 (1)	12 (2)	15 (3)	31 (7)
5	1 (1)	7 (0)	2 (0)	14 (3)	24 (4)
6	1 (0)	3 (2)	2 (0)	15 (2)	21 (4)

Data from age matched controls are given in parentheses.

Non parallel arrangements of cardiac muscle cells were not considered to represent disorganisation if they were in areas where cells normally converge at acute angles—ie, (*a*) the junction of the ventricular septum with the left and right ventricular free walls, (*b*) within trabeculations, (*c*) within scarred areas, and (*d*) at points of convergence of major muscle bundles or adjacent to interstitial spaces containing blood vessels.[3,4] Intraobserver variation was $<2\%$.

Data were expressed as the percentage of fields and means (SD) were compared by Student's non-paired *t* test.

Results

The figure shows the histological appearances of myocardial disarray in Noonan syndrome. Tables 2 and 3 show the total number of fields in which myocardial disarray was present in each patient. The percentage of disarray was significantly greater in patients with Noonan syndrome than in controls for both the ventricular septum (24·0 (5·7) *v* 3·8 (2·3), $p < 0{\cdot}0005$, 95% confidence interval 14 to 26·3) and the free wall (22·2 (6·8) *v* 2·4 (2·8), $p < 0{\cdot}005$, 95% confidence interval 11·4 to 28·2).

Table 3 *Disarray in left ventricular free wall*

Patient	*IA*	*IIA*	*IB*	*IIB*	*Total*
1	6 (0)	7 (1)	1 (0)	6 (0)	20 (1)
2	1 (0)	7 (0)	1 (0)	10 (7)	19 (7)
3	1 (0)	1 (1)	1 (0)	14 (0)	17 (1)
4	1 (0)	10 (1)	9 (1)	14 (1)	34 (3)
6	0 (0)	7 (0)	0 (0)	14 (0)	21 (0)

Data from age matched controls are given in parentheses.

Discussion

The characteristic phenotype of a group of patients with pulmonary stenosis was first described by Noonan.[5 6] Later it became apparent that left ventricular hypertrophy could occur in these patients.[7-9] The myocardial histopathology of this hypertrophy has not been characterised before because specimens are rare. We have collected a unique series of hearts and using a quantitative morphometric technique have shown that the extent of myocardial disarray was significantly greater in hearts from patients with Noonan syndrome and left ventricular hypertrophy than in age and sex matched controls. Because myocardial disarray affecting more than 5% of the sections obtained from the ventricular septum is a sensitive and specific marker for hypertrophic cardiomyopathy,[2-4] a histopathological similarity between hypertrophic cardiomyopathy and the hypertrophy of Noonan syndrome can be inferred. It was not possible to compare the extent of disarray directly as no age matched specimens from children with hypertrophic cardiomyopathy without Noonan syndrome were available. Death in hypertrophic cardiomyopathy is usually sudden and occurs in older children and adolescents, while death in Noonan syndrome is more often earlier and from cardiac failure.[8 10 11]

Hypertrophic cardiomyopathy is known to be inherited as an autosomal dominant disease in over 50% of cases,[12] but none of the parents (including one with the Noonan phenotype) who were screened echocardiographically showed hypertrophy. Noonan syndrome, although often sporadic, can be familial and is also inherited as an autosomal dominant trait.[13] Angiographic[3] and echocardiographic[14] evidence of transmission of left ventricular abnormalities from parent to child has been reported. Thus it can be argued that despite clinical differences hypertrophic cardiomyopathy and the ventricular hypertrophy associated with Noonan syndrome share a common genetic defect. Whether the two conditions are truly the same or whether hypertrophic cardiomyopathy is a heterogeneous group of diseases, as had been speculated,[15] can only be established when the molecular genetic defects are identified.[16]

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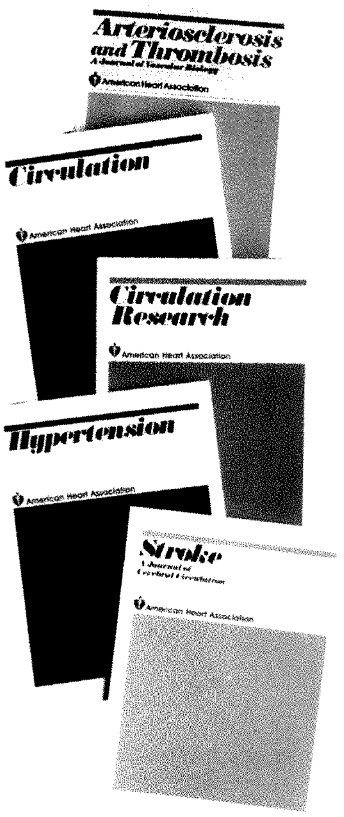

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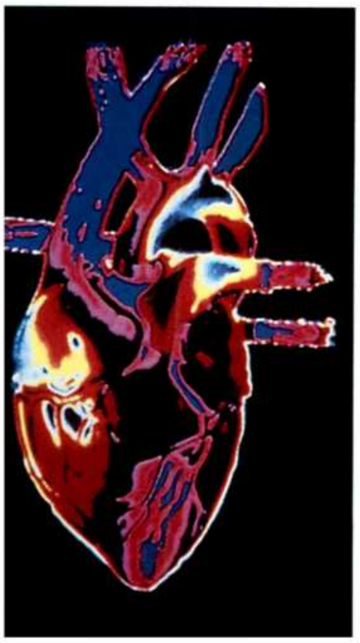

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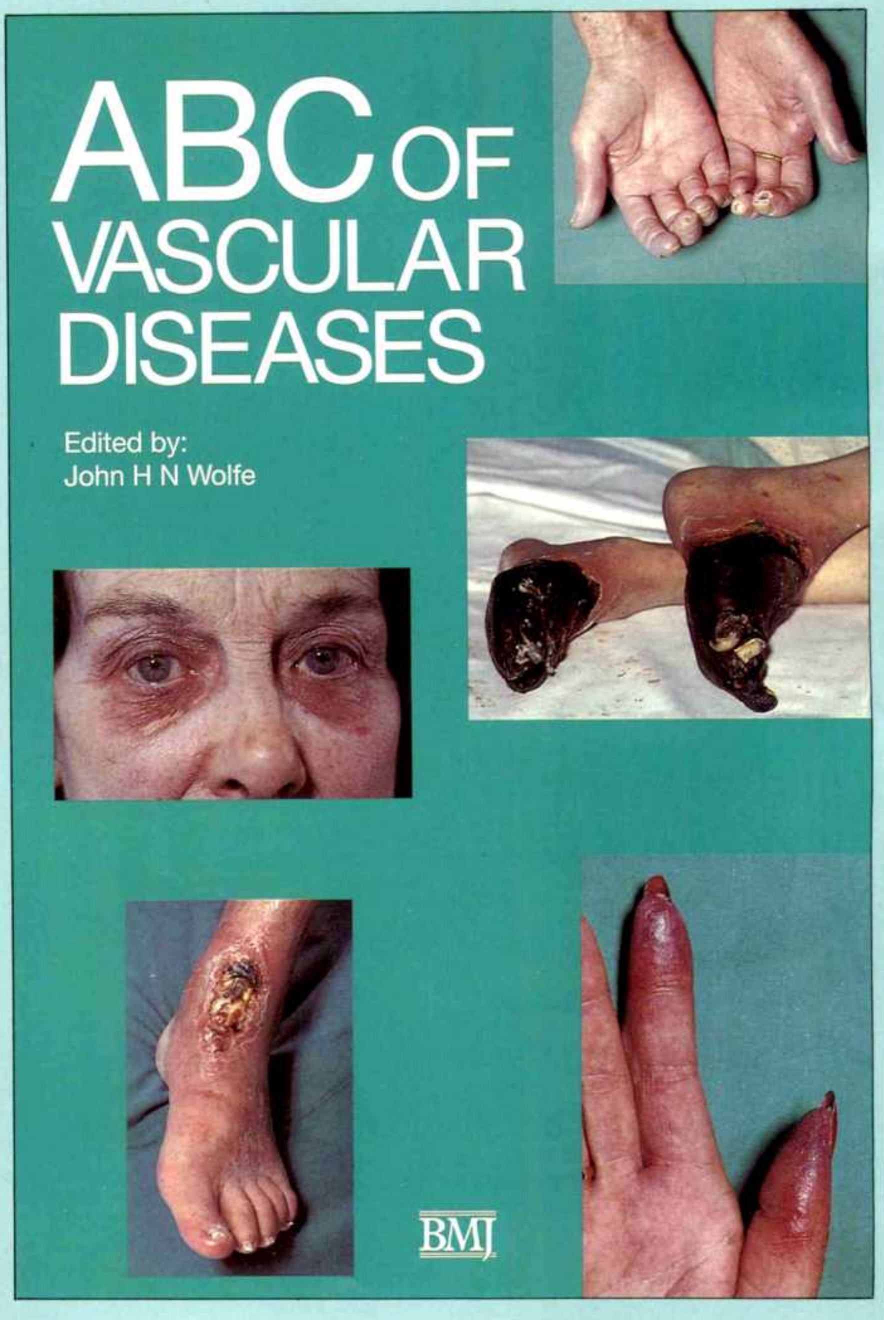

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Reappraisal of the coupling interval of ventricular extrasystoles as an index of ectopic mechanisms

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Abstract

***Objective*—A mathematical model of modulated ventricular parasystole based on the relation between the coupling interval and the preceding RR interval was developed in an attempt to distinguish between parasystolic automaticity and other mechanisms.**

***Mathematical model*—The relation between the coupling interval and the preceding RR interval was examined by plotting the coupling interval of each extrasystole against the preceding RR interval (coupling interval/RR diagram). The coupling interval/RR diagrams obtained from simulations with various modulation modes suggested that the parasystolic mechanism was likely when the dots representing extrasystoles appeared as discrete clusters. In contrast, a linear horizontal accumulation of dots indicated a non-parasystolic mechanism.**

***Clinical observation*—To verify the validity of the simulations, 24 hour electrocardiographic recordings from 60 patients with frequent ventricular extrasystoles (>1000/day) were analysed to determine whether the extrasystoles showed intrinsic periodicity. Intrinsic periodicity indicative of a parasystolic mechanism was seen in 14 (93%) of 15 patients in whom the coupling interval/RR diagram was characteristic of a parasystolic mechanism. When the coupling interval did not change (variability <200 ms) over a wide range of RR intervals (>700 ms) intrinsic periodicity was never identified (0/17). Parasystolic automaticity was the likely mechanism in 11 of the remaining 28 patients (39·3%) in whom coupling interval/RR diagrams were not definitive.**

***Conclusion*—These data indicate that definite patterns of coupling interval/RR diagrams can be used to distinguish between parasystolic and non-parasystolic mechanisms.**

(*Br Heart J* 1992;68:589–95)

Experimental and mathematical studies by Jalife and others on modulated parasystole[1–3] suggested a fixed coupling interval between parasystolic premature ventricular complexes and the preceding beat. Subsequent clinical observations[4–6] confirmed that the coupling interval of ventricular parasystole was not always randomly distributed and that both parasystolic and non-parasystolic mechanisms can show similar distributions of coupling intervals. Since then the diagnostic significance of the coupling interval has received little attention.

In a preliminary study in which we plotted the coupling interval of ventricular extrasystoles against the preceding RR interval we found that in some patients the coupling interval was consistent over a wide range of RR intervals. We assumed that a parasystolic mechanism was unlikely in these cases, but without objective evidence. To determine the likely and unlikely relations between the coupling interval and the preceding RR interval in parasystole we developed a mathematical model of modulated ventricular parasystole. The aim of this study was to determine the validity of using the relation between coupling and RR intervals as an index of ectopic mechanisms.

Patients and methods

We defined ventricular parasystole as an independent ectopic ventricular rhythm that has an inherent cycle length and is modulated by electrotonic influences but is not discharged by the dominant rhythm.[7]

MATHEMATICAL MODEL

The four variables in the mathematical simulation were the parasystolic cycle length, sinus cycle length, phase-response curve, and refractory period.

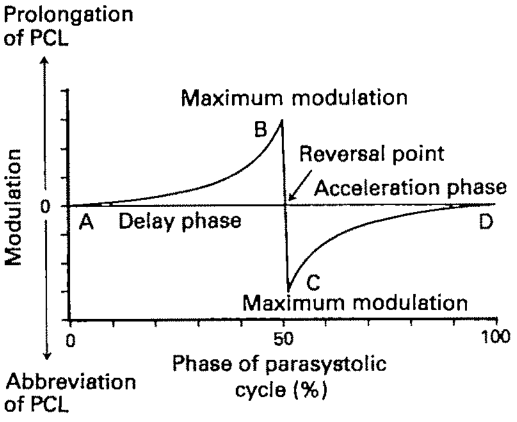

Figure 1 Biphasic phase-response curve for phase of parasystolic cycle (%) where a sinus beat falls and degree of modulation (%) of the parasystolic cycle length. The curve consists of a delay phase (A to reversal point) and an acceleration phase (reversal point to D). The occurrence of sinus beats during the delay phase prolongs the parasystolic cycle length (PCL), whereas during the acceleration phase it shortens the PCL.

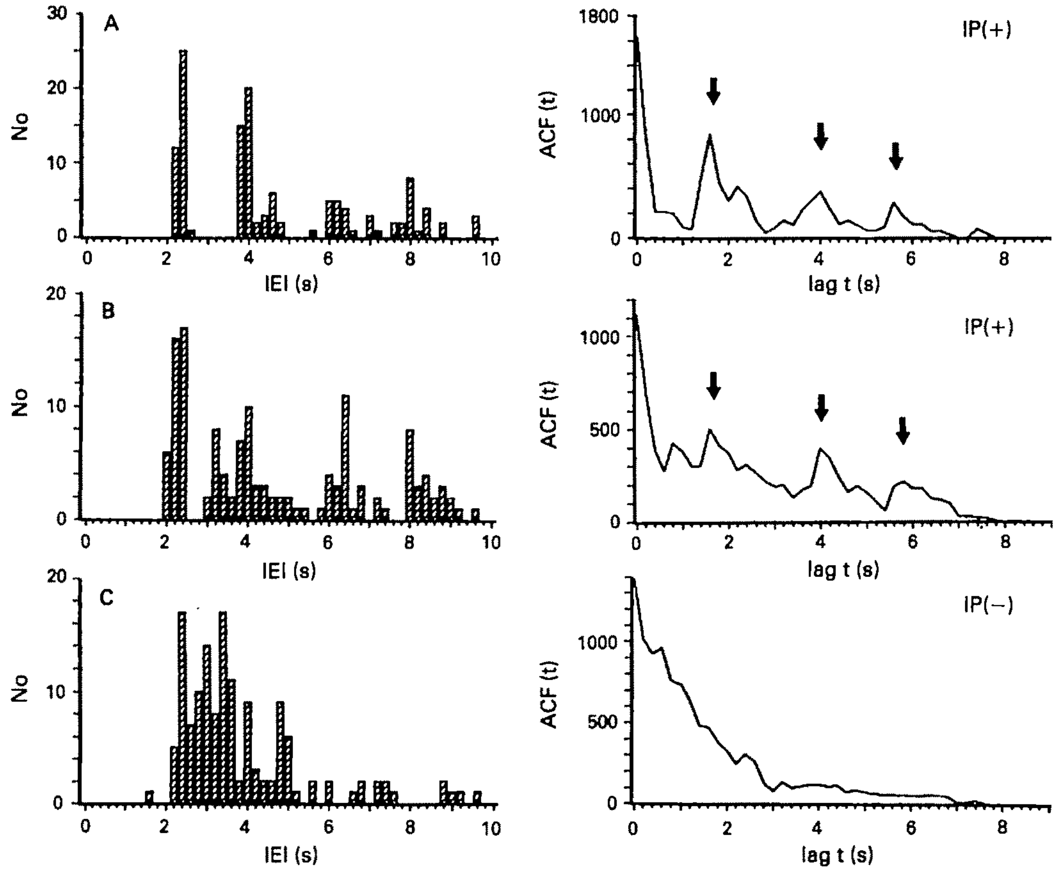

Figure 2 Examples of frequency histograms of inter-ectopic intervals (left) and autocorrelation function (ACF(t)) curves (right) in three patients. The frequency histograms show inter-ectopic intervals (IEI) and number of IEIs for every 0·2 s. The autocorrelation function is derived from the lag value T and the calculated ACF(t). A and B, show intrinsic periodicity (IP) of inter-ectopic intervals. Peaks of ACF(t) that repeatedly appeared at approximately every 2 s indicate inherent periodicity, that is, parasystolic automaticity (panels A and B, right). In panel C there is no inherent periodicity—that is, parasystolic automaticity was not the ectopic mechanism in this patient.

Parasystolic cycle length and sinus cycle length

Sinus and parasystolic discharges were set to start simultaneously at the begininning of simulation and were repeated with electrotonic modulation. The sinus cycle length was set at 400–1150 ms in 50 ms steps, and was shortened or lengthened by up to 20 ms to simulate physiological fluctuations such as respiratory sinus arrhythmia. Originally, the parasystolic cycle length was fixed at 2 seconds. We also tested variable parasystolic cyclè lengths, defined as 1·15 × (sinus cycle length) + 1080 ms on the basis of previous clinical observations.[8-10]. For each combination of variables we tested 784 parasystolic cycles.

Phase-response curve

The phase-response curve for modulation of the parasystolic cycle length by the sinus beat was biphasic in earlier biological and clinical studies.[2,4,5] The phase-response curve consists of a delay phase and an acceleration phase separated by the reversal point (fig 1). The degree of maximum prolongation of the parasystolic cycle length was set at 0, 1, 10, 20, 25, or 30% in the delay phase. Maximum shortening in the acceleration phase was set at 0, −1, −10, −20, −25, or −30% of the parasystolic cycle length.[2,4,5] The timing of the reversal point was not specifically defined. Instead, the point corresponding to the maximum prolongation in the delay phase was set as 20–80% of the parasystolic cycle in 10% steps. The distance between the point of maximum prolongation and that of maximum shortening was 1, 10, 20, 30, 40, 50, or 60% of the original parasystolic cycle length. The phase-response curve between the points of maximum modulation was always linear (B-C, fig 1), but the first and third portions (A-B and C-D (fig 1)) were hyperbolic curves or straight lines. The effects of two or more consecutive sinus beats falling during one parasystolic cycle were accumulated stepwise.[1]

Refractory period

The refractory period of exit from the parasystolic focus was estimated as 0·2 × (preceding RR interval) + 200 ms. Only parasystolic discharge outside the period of refractoriness associated with the preceding sinus beat became manifest and thus suppressed the subsequent sinus beat which would have occurred 0·4 × (sinus cycle length) + 100 ms or less after the manifest parasystole. These variables were selected from observations of our cases of apparent parasystole and from earlier reports.[9,10] The influence of parasystole on sinus cycle length was not included in the model because it could not be quantified. The coupling interval of each parasystolic beat was plotted against the preceding RR interval to show the relation between the two variables.

ANALYSIS OF CLINICAL OBSERVATIONS

Description of patients

We selected 60 consecutive 24 hour ambulatory electrocardiographic recordings with frequent ventricular extrasystoles (> 1000 per day). The recordings were excluded if repetitive forms were frequent (couplets, triplets, and short runs > 10% of total episodes), if extrasystoles were so loosely scattered that measurements of inter-ectopic intervals were useless, if there was

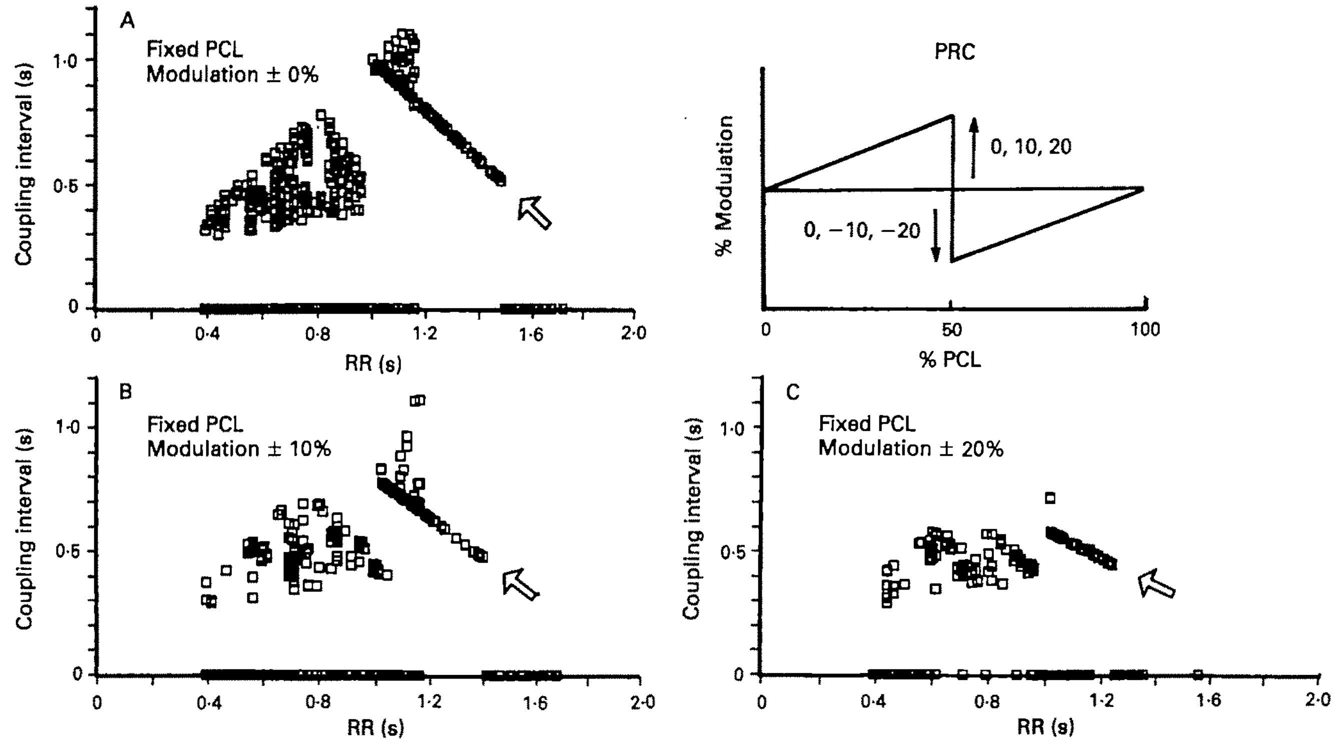

Figure 3 Diagrams of coupling interval/preceding RR interval (RR) acquired from a mathematical simulation of parasystole. The parasystolic cycle length (PCL) was fixed at 2 s. The degree of maximum modulation was set at ±0% (A), ±10% (B), and ±20% (C). Maximal modulation was set to occur at 50% and 51% of parasystolic cycle length. Each dot represents a single parasystolic complex. Dots on the abscissa—that is, coupling interval = 0—are discharges concealed by the refractory period of the preceding sinus beat. The dots were distributed as a cluster (left) and a linear cluster (arrow). PRC, phase-response curve.

atrial fibrillation or frequent premature supraventricular extrasystoles, or if the sinus cycle length varied by more than 400 ms.

We studied 30 men and 30 women aged 15–85 (mean (SD) 57·3 (13·7)). Three patients had dilated cardiomyopathy, three coronary artery disease, and two variant angina. Mitral valve prolapse was seen in one. Routine clinical examinations including echocardiography did not show organic heart disease in the remaining 51.

The 24 hour electrocardiographic recordings were analysed by computer (SCM 280, Fukuda Denshi, Tokyo, Japan). The coupling interval of each extrasystole was automatically plotted against the preceding RR interval. Extrasystoles with QRS configurations other than the dominant form were excluded from analysis. The likelihood of a parasystolic or non-parasystolic mechanism in each patient was assessed on the basis of the results of the mathematical model.

Evaluation of parasystolic automaticity

The diagnosis of parasystolic automaticity was based on the intrinsic periodicity in the appearance of extrasystoles. One hundred or more consecutive inter-ectopic intervals (<15 s) were measured during stable sinus rhythm (variation $<$ 10 per minute). Frequency histograms of the inter-ectopic intervals were constructed for every 200 ms [I(x) = incidence of inter-ectopic intervals between x seconds and x + 0·2 seconds]. To determine periodicity, the autocorrelation function ACF(t) was calculated by the following formula:

$$\mathrm{ACF}(t) = \sum_{\kappa=0}^{75} [I(0{\cdot}2k) \times I(0{\cdot}2k+t)],$$

where t is the lag of the autocorrelation function.[11] From the upper limit of the summation, it can be seen that as lag t increases, the number of samples available for calculation decreases. This leads to a reduction in the magnitude of ACF peaks as t increases. Figure 2 shows examples of frequency histograms of inter-ectopic interval and the corresponding ACF(t). Periodic peaks of ACF(t), which were independent of sinus cycle length (fig 2A and B), were diagnostic of parasystole.

STATISTICAL ANALYSIS

Data are presented as means (SD). Differences in proportions were analysed by the generalised χ^2 test. The unpaired t test was used to compare mean values. A probability (p) value $<0{\cdot}05$ was regarded as significant.

Results

MATHEMATICAL MODEL

Figures 3–5 are examples of coupling interval/RR diagrams simulated with the mathematical model of parasystole. Figure 3 shows the effects of the degree of modulation on the relation between the two variables with a fixed parasystolic cycle length. When the parasystolic cycle length was independent of sinus discharge—

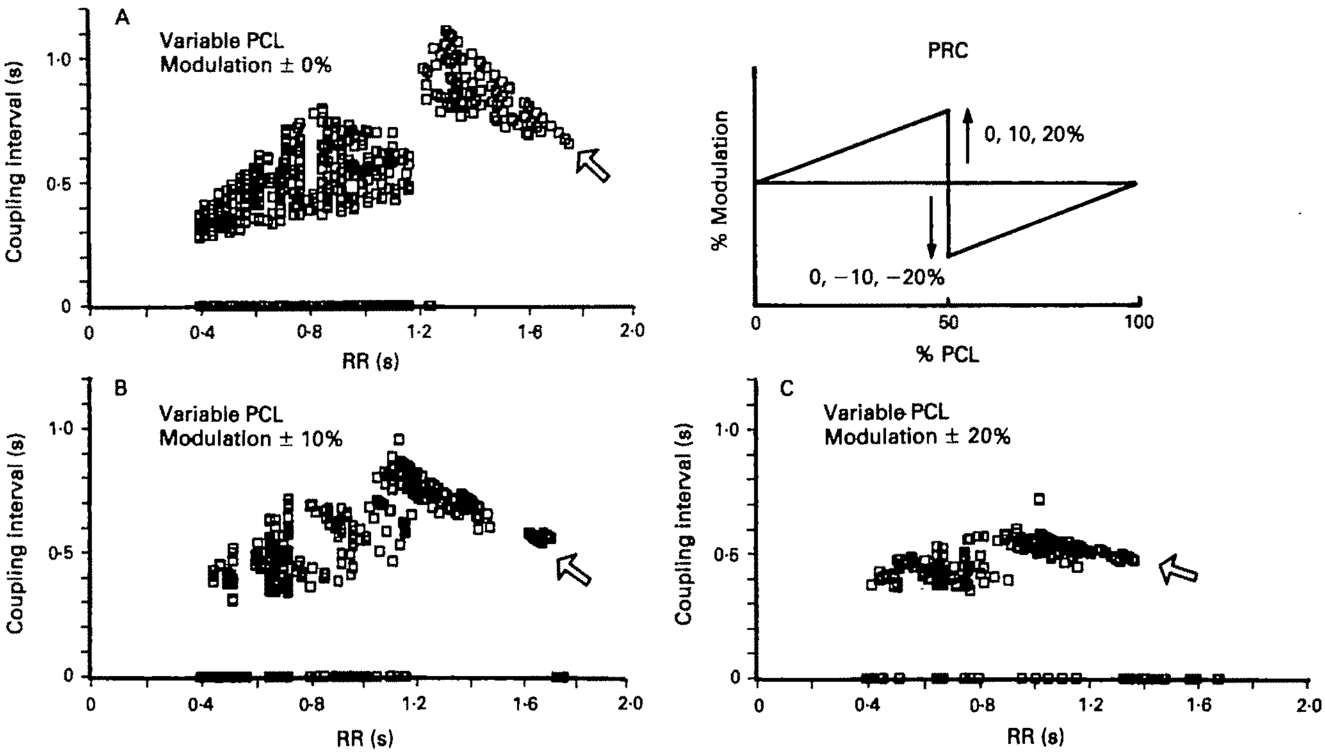

Figure 4 Coupling interval/RR diagrams acquired from the mathematical simulation of parasystole with variable parasystolic cycle lengths (1·15 × (sinus cycle length) + 1080 ms). The degree of maximum modulation is indicated. Maximal modulation was set to occur at 50% and 51% of parasystolic cycle length. The cluster of dots on the right hand side remained (arrows). See legend to fig 3 for abbreviations. –

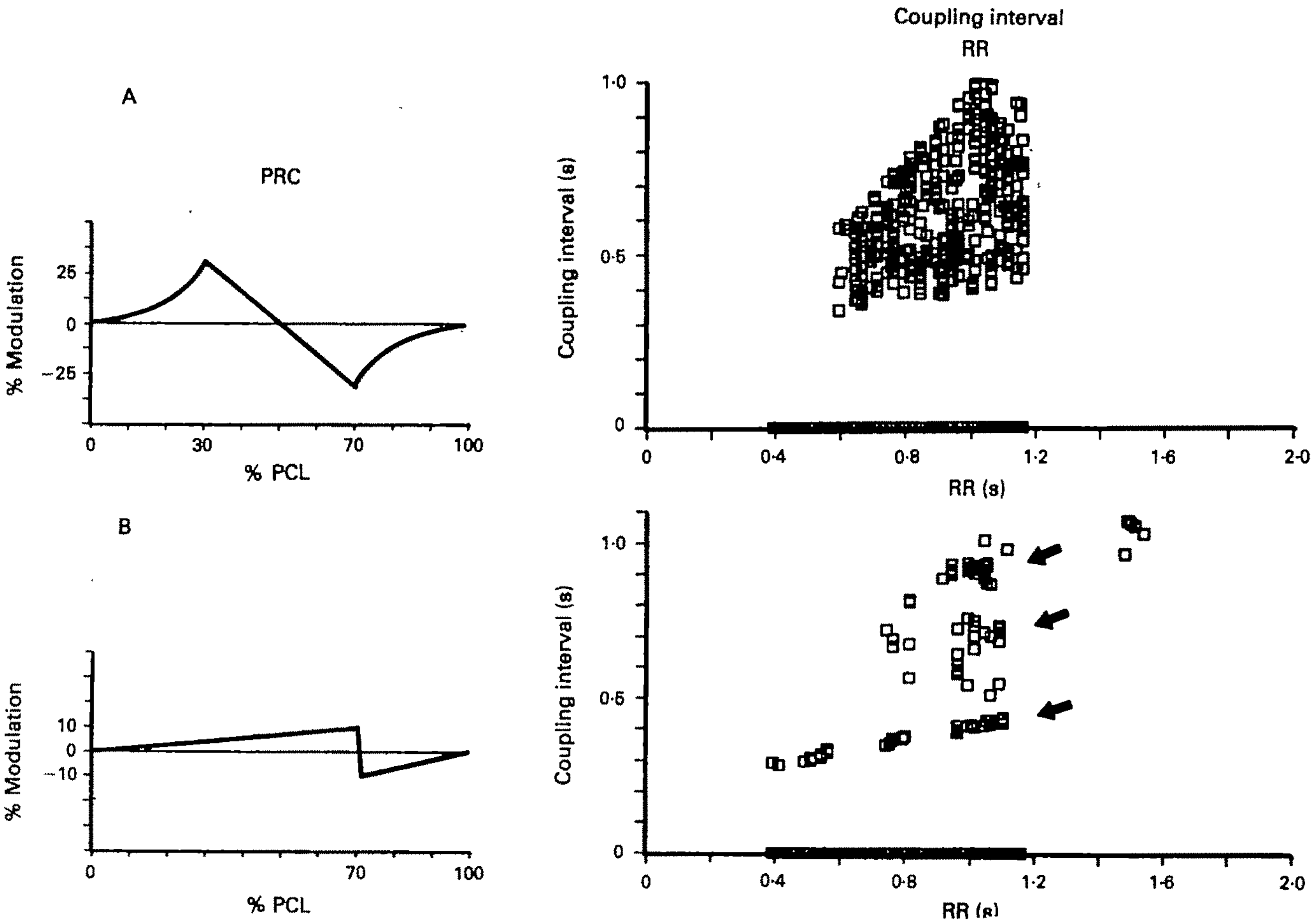

Figure 5 Coupling interval/RR diagrams from the mathematical models with different phase-response curves (PRC). (A) a coupling interval/RR diagram without a dot-free space, (B) an example in which the coupling intervals clustered around three values (0·4, 0·7, and 0·9 s) (arrows). See legend to fig 3 for abbreviations.

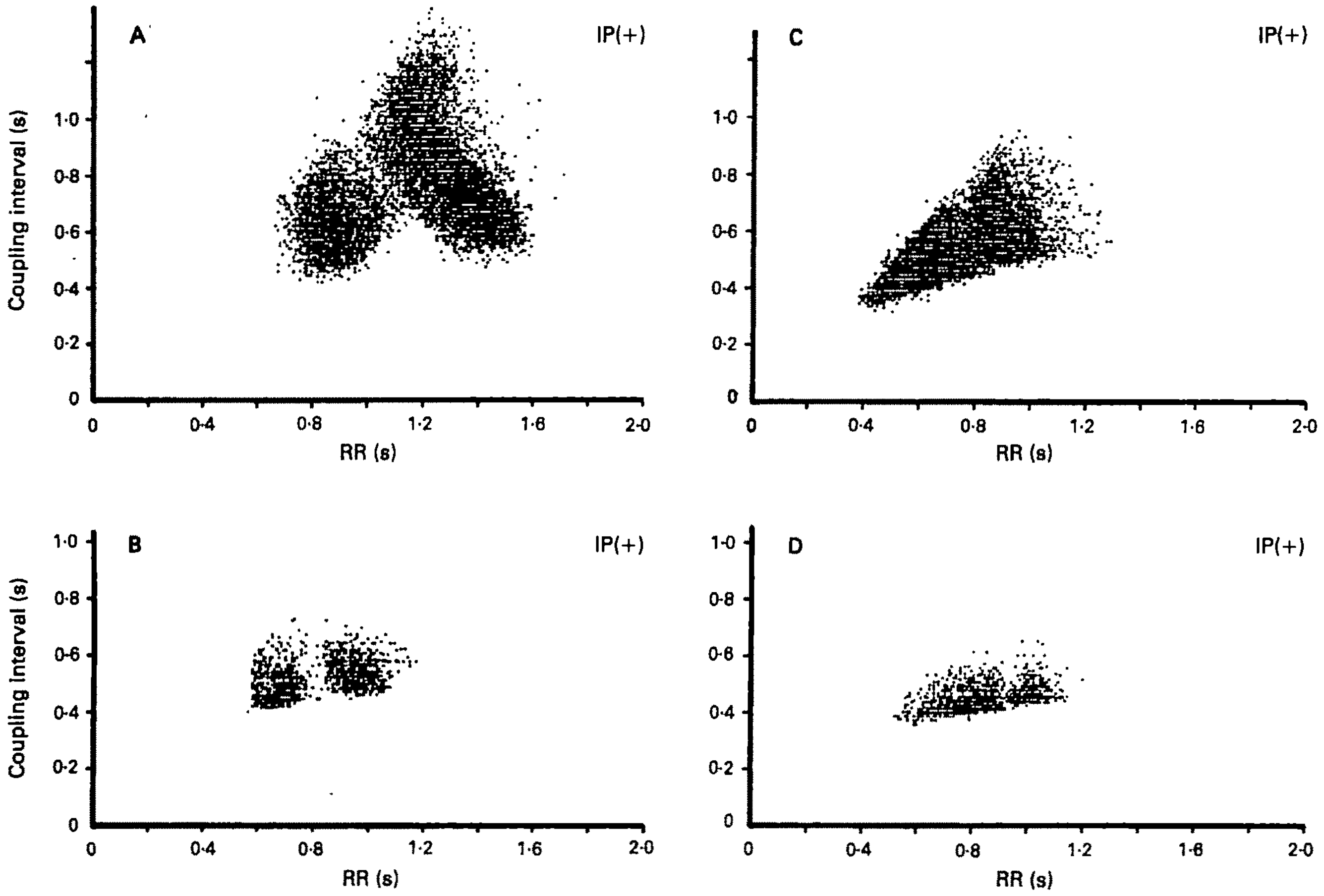

Figure 6 Examples of relation between the coupling interval and the preceding RR interval obtained from 24 hour electrocardiographic recordings from four type 1 patients. There was evidence of intrinsic periodicity (IP) of extrasystoles in all 4. Figure 2A shows the frequency histogram of inter-ectopic intervals corresponding to fig 6C. See legend to fig 3 for abbreviations.

that is no modulation—the coupling interval/RR diagrams showed a linear concentration of dots (arrow, fig 3A). Because the sum of the coupling and RR intervals that constituted this linear accumulation was equal to the parasystolic cycle length (2 s), it was apparent that these dots were associated with an ectopic-sinus-ectopic sequence with a compensatory pause. Although the slope and length gradually changed with changes in modulation, a right-sided linear accumulation remained (fig 3B and C). More extensive modulation—that is +25 to −25% or more, concealed most of the parasystolic discharge (not shown).

Figure 4 shows the effect of a variable parasystolic cycle length on the relations between coupling interval and RR interval. A linear diagonal accumulation of dots was present whatever the degree of modulation (arrows). The distinguishing difference in the coupling interval/RR diagrams between fixed (fig 3) and variable (fig 4) parasystolic cycle lengths was the density of dots along the diagonal.

Coupling interval/RR diagrams without a linear concentration of dots were rarely obtained except with certain phase-response curves (fig 5A). As in the earlier study[2] coupling intervals clustered at two or three widely separated positions with some phase-response curves (fig 5B). However, this distintive distribution of dots was exceptional and disappeared with only slight modification of the phase-response curve.

Thus by arranging the variables of the model various coupling interval/RR diagrams could be produced. However, a horizontally linear accumulation of dots over a wide range of RR intervals, corresponding to a consistent coupling interval, was not seen.

APPLICATION OF OBSERVATIONS IN THE MATHEMATICAL MODEL TO THE DIAGNOSIS OF ECTOPIC MECHANISMS OF CLINICAL ARRHYTHMIAS

Extrapolating the observations in the model to clinical arrhythmias, we considered that a parasystolic mechanism was likely when dots appeared as two or more clusters separated by dot-sparse areas. There are dot-sparse spaces in the left-sided cluster in fig 3A and 3B and fig 4A, B, and C. However, because the occurrence and sites of these dot-sparse spaces were not constant, we did not regard this observation as a characteristic of the parasystolic mechanism.

CLINICAL OBSERVATIONS

Clinical ventricular extrasystoles were divided into three groups.

Type 1—when dots in the coupling interval/RR diagram were divided by dot-sparse space(s) parasystolic automaticity was considered to be the mechanism involved. Figure 6 shows examples of this type. Fifteen patients

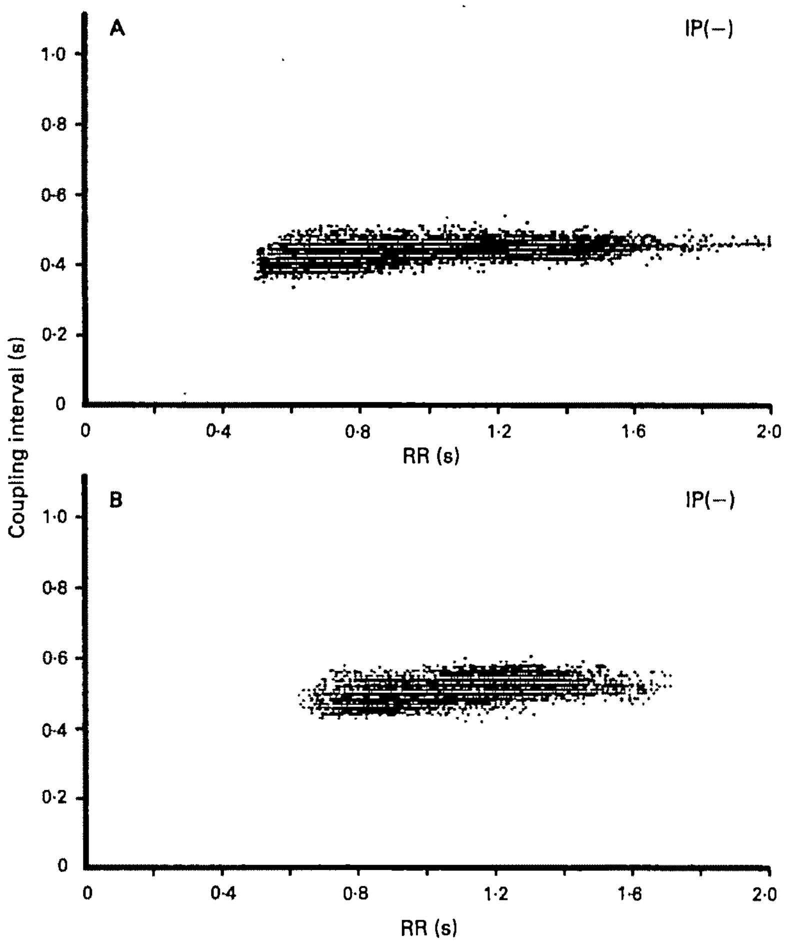

Figure 7 Coupling interval/RR diagrams from type 2 patients in which there was no intrinsic periodicity (IP) of the extrasystoles. The horizontal linear clustering was unique to this group. See legend to fig 3 for abbreviations.

had a distinctive distribution of this type. In 14 (93%) of these 15 recordings we saw intrinsic periodicity of the extrasystoles that was suggestive of parasystolic automaticity. The possible parasystolic cycle length ranged from 1·5 to 2·7 s (2·0 (0·3) s). In the remaining recording, inter-ectopic intervals clustered around three and six seconds but not around nine seconds. The diagnosis of parasystolic automaticity was not definite in this case.

Type 2—If there was a horizontal accumulation of dots over a wide range of RR (> 700 ms) non-parasystolic mechanisms were considered to be the most likely cause of the extrasystoles (fig 7). Seventeen patients had plots of this type. Intrinsix periodicity of extrasystoles was never seen in this group.

Type 3—The remaining 28 patients make up a third group (fig 8). Because the clusters of dots were divided into upper and lower groups but not into right and left ones in fig 8B, this diagram was not considered specific for the parasystolic mechanism. The extrasystoles in fig 8C were diagnosed as parasystolic automaticity, while those in figs 8A and B were not. Frequency histograms of the inter-ectopic interval and ACF(t) indicated parasystolic automaticity as the mechanism of the extrasystoles in 11 (39%) of these 28 patients. The possible parasystolic cycle length ranged from 1·5 s to 3·0 (2·0 (0·4)) s (not significant compared with type 1).

Inter-group differences in the incidence of intrinsic periodicity were significant (p < 0·0001).

Discussion

INTERPRETATION OF RESULTS

Both parasystole and reentrant extrasystoles can show fixed coupling to the preceding beat.[2,4,9] In an experimental study triggered activity caused bigeminy with fixed coupling.[12] Therefore, analysis of the coupling interval alone seems of limited value in determining the underlying mechanisms. In our study, an extremely high incidence of intrinsic inter-ectopic periodicity was shown in type 1 patients. Type 2 patients did not show such periodicity. Neither the relation between coupling and RR intervals nor the measurement of the interval between extrasystoles provided a definite diagnosis of the ectopic mechanisms. However, the coupling interval/RR diagram was an accurate indicator of parasystolic and of non-parasystolic mechanisms in patients with type 1 or type 2 patterns: the diagnoses based on the two methods were the same in 31 of the 32 patients.

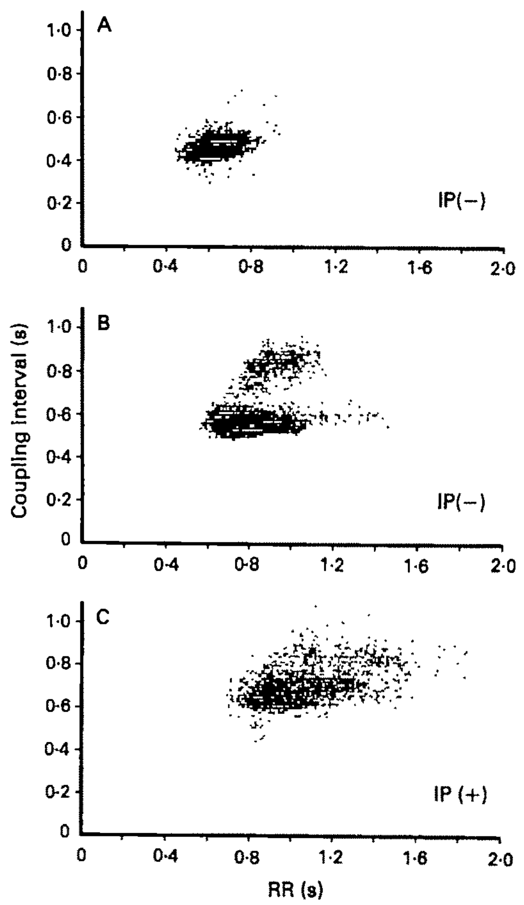

Figure 8 Coupling interval/RR diagrams from type 3 patients. There was intrinsic periodicity (IP) of extrasystoles in patient C. Figure 2C is the frequency histogram of inter-ectopic intervals for patient A and fig 2B is the frequency histogram for patient C. See legend to fig 3 for abbreviations.

Michelson *et al* found that the response of the coupling interval to changes in sinus cycle length induced by exercise was not uniform even if coupling was temporarily fixed.[13] The incidence of parasystolic automaticity in their study was smaller than that in the present study (10% *v* 43·3%). Differences in the number of extrasystoles analysed, in the range of sinus cycle lengths, and in the definition of parasystole may explain this discrepancy. Nevertheless, both their results and ours showed that the relation between the coupling and RR intervals indicated the ectopic mechanism.

EXPLANATION OF RESULTS

Moe *et al* reported stable entrainment of parasystolic ventricular extrasystoles causing bigeminy and trigeminy in a mathematical model.[2] The ultimate pattern was the same irrespective of the starting condition. Also, they found that the coupling interval clustered at long or short intervals, even if it was not fixed in a strict sense. These observations indicated that the range of coupling intervals in parasystole is inherently determined by the combination of sinus and parasystolic cycle lengths and by the mode of modulation.

Figure 3 indicates that the ectopic-sinus-ectopic sequences that usually appeared as bigeminal group beating might generate an additional cluster of dots at RR intervals longer than 1·15 seconds. The degree of modulation may be reflected in the slope of this right-sided linear, diagonal cluster. Clearly, the sum of the coupling interval and RR for the ectopic-sinus-ectopic sequences is identical to the parasystolic cycle length (2 s) when modulation is absent. When modulation is present, the slope of right-sided linear accumulation tends to be less steep. This may be because the degree of shortening of parasystolic cycle length correlates negatively with RR, making the sum of the coupling interval and RR greater at a longer RR when the sinus beat occurs predominantly in the acceleration phase of the parasystolic cycle during bigeminal group beating.

METHODOLOGICAL CONSIDERATIONS

The modulation mode varies from patient to patient.[4 5 9] Oreto *et al* reported a more complex modulation—ie, the triphasic phase-response curve.[14] If the correlation beteen parasystolic and sinus cycle lengths is more linear than we estimated, consistently fixed coupling would be possible. Because the number of combinations of variables was limited in the present study, we cannot exclude the possibility of other types of relations between coupling and RR intervals. The influence of intervening parasystole on sinus rhythm was not included in our model. If a two-way interaction between parasystolic and non-parasystolic complexes is important our results would be affected.

The method used here to detect parasystolic automaticity is not an established one. Although we believe that the autocorrelation function ACF(t) made the intrinsic periodicity of extrasystoles apparent, parasystolic automaticity might sometimes have been overlooked or overdiagnosed.

Finally, our criteria for the diagnosis of parasystole and non-parasystole from the coupling interval/RR diagram were not quantitative. Complicated criteria do not seem to increase the diagnostic sensitivity, because non-specific relations between the two variables, as shown in fig 8, are not infrequent. Further studies are needed to establish a simple criterion that gives excellent sensitivity as well as excellent specificity.

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Different distribution of abnormal endocardial electrograms within the right atrium in patients with sick sinus syndrome

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Abstract

***Background*—Prolonged and fractionated right atrial endocardial electrograms are characteristic of paroxysmal atrial fibrillation (idiopathic or associated with sick sinus syndrome). The distribution of these abnormal atrial electrograms within the right atrium and the way it is related to the likelihood that patients with sick sinus syndrome will develop paroxysmal atrial fibrillation was studied.**

***Methods*—Endocardial catheter mapping of the right atrium during sinus rhythm was performed in 41 control patients with normal sinus node function and without paroxysmal atrial fibrillation, in 33 patients with sick sinus syndrome but without tachycardia, and in 27 patients with sick sinus syndrome and paroxysmal atrial fibrillation (group 3). The bipolar electrograms were recorded at 12 sites in the right atrium and an abnormal atrial electrogram was defined as lasting ≥100 ms and/or showing eight or more fragmented deflections.**

***Results*—1195 atrial endocardial electrograms were assessed and quantitatively measured. In patients with sick sinus syndrome and paroxysmal atrial fibrillation 54% of the abnormal atrial electrograms were recorded from the high right atrium, 28% from the mid right atrium, and 18% from the low right atrium. However, in patients with sick sinus syndrome without tachycardia 78% of the abnormal atrial electrograms were recorded from the high right atrium and 22% from the mid right atrium. No abnormal electrograms were recorded from the low right atrium.**

***Conclusions*—In patients with sick sinus syndrome without tachycardia abnormal atrial electrograms generally came from the high right atrium but in patients with sick sinus syndrome and paroxysmal atrial fibrillation abnormal atrial electrograms were more widely distributed in the right atrium. In patients with sick sinus syndrome the greater the extent of the compromised atrial muscle, the greater the likelihood that paroxysmal atrial fibrillation will develop.**

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Fragmented and continuous ventricular electrical activity was recorded from infarcted ventricular muscle in canine hearts[1 2] and in patients with ischaemic heart disease.[3–5] The electrograms are fractionated because muscle fibers are separated by scar tissue, which causes fragmented, slow, and anisotropic conduction.[6]

With intra-atrial catheter mapping we showed that a prolonged and fractionated atrial electrogram is characteristic of paroxysmal atrial fibrillation (either idiopathic or associated with sick sinus syndrome).[7] However, the sites in the right atrium where abnormal atrial electrograms are generated in patients with sick sinus syndrome have not been described. About 15–40% of patients with sick sinus syndrome develop paroxysmal atrial fibrillation[8 9] while the remainder do not. We wondered whether this reflected a difference in the extent and distribution of abnormal atrial electrograms in patients with sick sinus syndrome. We designed a study (*a*) to determine the sites in the right atrium of patients with sick sinus syndrome at which electrical activity is likely to be abnormal and (*b*) to find a relation between the distribution of abnormal atrial electrograms and the likelihood that paroxysmal atrial fibrillation will develop in patients with sick sinus syndrome.

PATIENTS

One hundred and one patients referred to the Nagasaki University Hospital for electrophysiological evaluation of their arrhythmias underwent right atrial endocardial mapping in sinus rhythm during investigation. No patients with hypothyroidysm, congestive heart failure, organic heart disease, or cerebrovascular accidents were admitted to the study. None of the patients had had a recent myocardial infarction or operation. Neither drug treatment nor serum electrolyte disturbances were found to be related to the genesis of the sinus node dysfunction in our study patients. No patient in whom echocardiography showed atrial enlargement was included in this investigation.

We studied three groups of patients. Group 1 was 41 patients (19 women and 22 men) with normal sinus node function and without paroxysmal atrial fibrillation (age 41–83 years, mean (SD) 64·5 (10·5)). Electrophysiological study was performed because of atrioventricular nodal reentrant tachycardia in 20 patients, advanced or complete atrioventricular block in 19 patients, and ventricular tachycardia in two patients. Because of their known predisposition to develop paroxysmal atrial fibrillation, patients with the Wolff-Parkinson-White syndrome[10–12] were not included in this group. The sinus node recovery time ranged from 0·72 to 1·34 s (mean (SD) 1·07 (0·15) s). Group 2 consisted of 33 patients (17 women and 16 men) with sick sinus syndrome but without tachycardia (age 42–81 years, mean (SD) 63·7 (9·3)). Eleven patients had persistent and unexplained sinus bradycardia (<50 beats/min) on the resting electrocardiogram,[13] with fewer than 70 thousand beats per 24 hours on ambulatory Holter monitor recordings.[14] The other 22 patients had documented episodes of sinoatrial block or sinus arrest with atrioventricular junctional or ventricular escape depolarisation.[15 16] The sinus node recovery time ranged from 1·15 to 6·88 s (mean (SD) 2·93 (1·9) s). There was no clinical evidence of paroxysmal atrial fibrillation in any of these patients. Care was taken to avoid false diagnosis of sinoatrial block in the presence of premature non-conducted atrial depolarisation. Group 3 comprised 27 patients (18 women and nine men) (age 49–81 years, mean (SD) 66·7 (8·9)) with both sick sinus syndrome and paroxysmal atrial fibrillation, that is, the so-called bradycardia-tachycardia syndrome. All patients in this group had confirmed paroxysmal atrial fibrillation. The sinus node recovery time ranged from 1·20 to 9·28 s (mean (SD) 4·23 (2·2) s). Sinus node dysfunction in the patients in groups 2 and 3 and the paroxysmal atrial fibrillation of the patients in group 3 were confirmed by conventional electrocardiography, bedside electrocardiographic monitoring, and/or at least two 24 hour ambulatory electrocardiographic Holter recordings. The sinus node recovery time was measured in all patients after atrial overdrive pacing[17 18] at rates of 70–210/min for a minute at each level. There was no significant age difference among patients in the three groups.

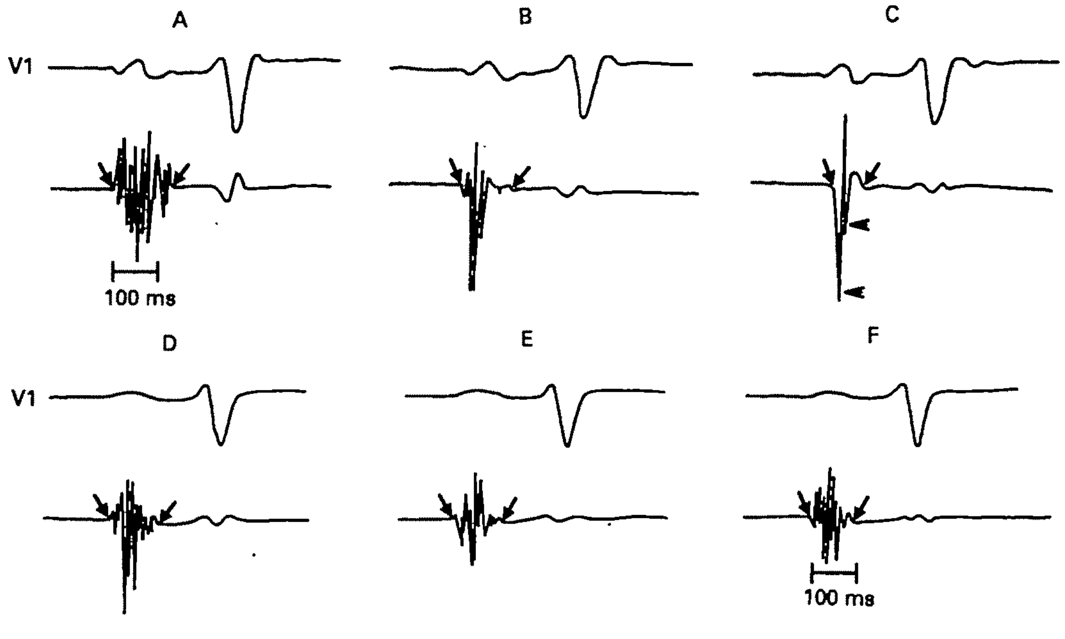
ELECTROPHYSIOLOGICAL STUDY

All patients were studied in the postabsorptive, non-sedated state after they had given informed consent. Electrophysiological evaluation was performed after approval of the study plan by the regional ethics committee. All drugs were stopped at least 72 hours before the procedure. Two bipolar catheter electrodes (No 6F USCI) were inserted percutaneously into the femoral and subclavian veins and were advanced into the right atrium under fluoroscopic guidance. The distance between the electrodes was 10 mm and the electrode ring was 2 mm in diameter.

All the right atrial endocardial electrograms were recorded during sinus rhythm by bipolar electrodes at a fixed gain setting, accompanied by a 0·2 mV = 3 mm calibration signal, and were filtered at 50–1000 Hz. The baseline of recordings was stable for each patient. The atrial endocardial electrograms together with the monophasic action potential and three surface electrocardiograms (I, aVF, and V1) were displayed on a multichannel oscilloscope (Fukuda-Denshi polygraph MIC-8800T) and simultaneously recorded at a paper speed of 100 mm/s on a 12 channel, ink jet recorder (Siemens-Elema 804). All data were stored on magnetic tape throughout the entire electrophysiological study. The atrial electrograms remained constant and reproducible at each recording site in individual patients.

The bipolar electrograms were recorded from 12 sites in the right atrium in each patient. The intra-atrial catheter mapping procedure is described elsewhere.[7] The high and middle atrial sites were mapped by the catheter inserted through the femoral vein and the low atrial sites were mapped through the subclavian vein. No complications were noted in any patient as a result of these manoeuvres. Stability was ensured by recording at each site for a minimum of 8–15 s and by using a looped catheter. The position of the catheter tip was verified by multiple or single plane fluoroscopy in the presence of at least two experienced physicians familiar with the right atrial endocardial mapping procedure. All the instruments were properly isolated and earthed.

Figure 1 Six atrial electrograms recorded at different right atrial sites in two patients with sick sinus node syndrome (A, B, and C in a group 2 patient; D, E, and F in a group 3 patient). Diagonal arrows represent the onset and offset of local electrical activity and horizontal arrows the downward deflections. See text for details.



Total number (%) of abnormal atrial electrograms in each of the three groups

	Number of electrograms	*Normal electrograms (%)*	*Abnormal electrograms (%)*
Group 1	479	465 (97·08)	14 (2·92)
Group 2	391	355 (90·79)	36 (9·21)
Group 3	325	246 (75·69)	79 (24·31)

Group 3 *v* group 1, $p < 0\cdot0001$; Group 3 *v* group 2, $p < 0\cdot0001$; Group 2 *v* group 1, $p < 0\cdot0002$.

DEFINITIONS

The duration of an atrial electrogram was defined as the time from the beginning of the earliest electrical activity that deviated from the stable baseline value to the last point of the atrial electrogram at which the baseline value was crossed. The number of fragmented deflections was measured by counting the number of downward deflections[7] (fig 1).

In an earlier study[7] we defined quantitative standards for normal bipolar electrograms. An abnormal atrial electrogram was defined as lasting $\geqslant 100$ ms or as eight or more fragmented deflections or both.

Figure 1 shows six examples of the measurements on the atrial electrograms recorded from different right atrial endocardial sites in a patient with sick sinus syndrome but without tachycardia (A, B, and C) and in a patient with both sick sinus syndrome and paroxysmal atrial fibrillation (D, E, and F). Figure 1A was recorded from the high lateral right atrium and shows an abnormal atrial electrogram 130 ms in duration with 10 fragmented deflections. Figure 1B was recorded from the mid lateral right atrium and shows an abnormal atrial electrogram 110 ms in duration with six fragmented deflections. Figure 1C was recorded from the low lateral right atrium and shows a normal atrial electrogram 80 ms in duration with two fragmented deflections. Figure 1D was recorded from the high posterior right atrium and shows an abnormal atrial electrogram 110 ms in duration with nine fragmented deflections. Figure 1E was recorded from the mid posterior right atrium and shows an abnormal atrial electrogram 105 ms in duration with eight fragmented deflections. Figure 1F was recorded from the low posterior right atrium and shows an abnormal atrial electrogram 100 ms in duration with eight fragmented deflections.

	Lateral	Anterior	Posterior	Medial		
High RA	○○ ▲▲▲▲▲▲ ●●●●●●●●●●●●●●●●	○○ ▲▲▲▲▲▲ ●●●●●●●	○○○○○○ ▲▲▲▲▲▲▲▲▲▲▲▲▲ ●●●●●●●●●●●●●	○○○ ▲▲▲ ●●●●●●●	13 28 43	84
Mid RA	▲▲ ●●●●●●●●	▲ ●●●	▲▲▲▲ ●●●●●●●	▲ ●●●●	0 8 22	30
Low RA	○ ●●●●	●●	●●	○ ●●●●●●	2 0 14	16
	39	21	45	26		130

○ Group 1 ▲ Group 2 ● Group 3

Figure 2 Sites in the right atrium with abnormal atrial electrograms in the three groups. One symbol represents one abnormal atrial electrogram. See text for details.

STATISTICAL ANALYSIS

The duration of and the number of fragmented deflections on the atrial electrograms were assessed at each site by at least two independent observers. A minimum of five to eight atrial complexes of uniform configuration were assessed at each of the 12 sites of the atrium, and when interobserver measures did not accord a mean value was calculated. Prevalence was determined by χ^2 test.

Results

We assessed 1195 atrial endocardial electrograms (table) (479 in group 1, 391 in group 2, and 325 in group 3). There were 14 (2·92%) abnormal atrial electrograms in group 1, 36 (9·21%) in group 2, and 79 (24·31% in group 3. (group 3 *v* group 1, $p < 0\cdot0001$; group 3 *v* group 2, $p < 0\cdot0001$; group 2 *v* group 1, $p < 0\cdot0002$).

SITE OF ORIGIN OF ABNORMAL ATRIAL ELECTROGRAMS

Figure 2 shows the sites in the right atrium where abnormal electrograms were seen in the three groups. Forty three (54%) of the 79 abnormal atrial electrograms in group 3 were seen at the high right atrium, 22 (28%) at the mid right atrium, and 14 (18%) at the low right atrium (high right atrium *v* mid right atrium, $p < 0\cdot05$ and high right atrium *v* low right atrium, $p < 0\cdot002$). There was no significant

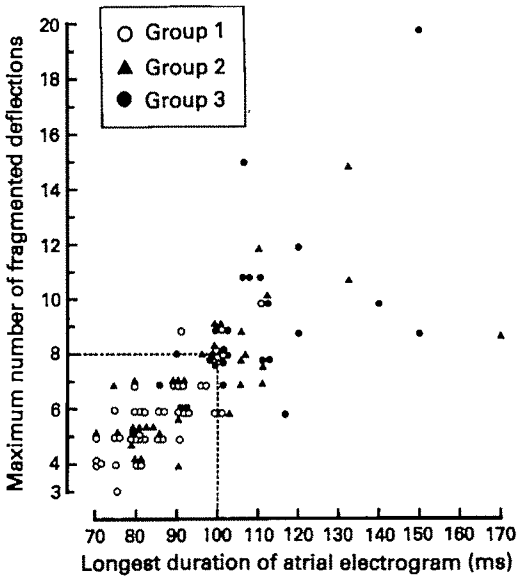


Figure 3 Longest duration and the maximal number of fragmented deflections of atrial electrograms at 12 sites in the right atrium in each patient in the three groups. One symbol represents one patient. The broken lines indicate the limits of normality. Symbols on the lines or outside the square formed by the lines are abnormal results.

difference in the number of abnormal electrograms between the mid and low right atrium in group 3 patients. Of the 43 abnormal electrograms at the high right atrium, 67% were recorded from the posterolateral high right atrium. Seventy eight percent of the patients in group 3 with abnormal electrograms had them in the posterolateral high right atrium.

We recorded 36 abnormal atrial electrograms in group 2 patients; 28 (78%) in the high right atrium, eight (22%) in the mid right atrium, and none in the low right atrium (high right atrium *v* mid right atrium, $p < 0{\cdot}01$; mid right atrium *v* low right atrium, $p < 0{\cdot}02$; high right atrium *v* low right atrium, $p < 0{\cdot}0001$). Of the 28 abnormal electrograms at the high right atrium, 68% were recorded from the posterolateral high right atrium. In group 2 88% of the patients with abnormal electrograms had them recorded in the posterolateral high right atrium.

Figure 3 shows the longest duration and the greatest number of fragmented deflections for atrial electrograms recorded at the 12 right atrial sites in each patient in the three groups.

Discussion

Fractionated electrograms were recorded from areas of canine ventricular tissue where so much fibrous tissue separated the muscle fibres from each other that the fibres were no longer arranged in parallel.[19] They were also recorded from canine[20] and human[21] atrial muscle in which the muscle fibres were widely separated and their orientation distorted by connective tissue to such a degree that the number of intercellular connections was reduced. This could increase resistance to current flow and thereby slow conduction.

A prolonged and fractionated atrial electrogram may reflect unsynchronised local electrical activity related to a delayed and non-uniform anisotropic conduction through a diseased atrial muscle. Therefore, abnormal electrograms indicate areas of altered anatomy and conduction where reentrant arrhythmias are likely to develop.

We found a significantly greater number of abnormal endocardial electrograms in the high right atrium of patients with sick sinus syndrome irrespective of the presence or absence of paroxysmal atrial fibrillation. However, there was no significant difference between the number of abnormal electrograms recorded from the mid and low right atrium in patients with sick sinus syndrome and paroxysmal atrial fibrillation, suggesting that in these patients the electrophysiological abnormality of the atrial muscle was more diffuse. In the patients with sick sinus syndrome alone no abnormal endocardial electrograms were recorded from the low right atrium, which suggested a more localised electrophysiological abnormality.

Pathological studies showed that patients with sinoatrial block without tachycardia had disease localised to the sinus node and its approaches, whereas patients with the bradycardia-tachycardia syndrome had a more diffuse lesion of the atrium.[22] Our electrophysiological studies accorded with these histological findings in that we found that abnormal atrial electrograms were generally localised to the high right atrium in the vicinity of the sinus node in patients with sick sinus syndrome without tachycardia whereas in patients with both sick sinus syndrome and paroxysmal atrial fibrillation they were more widely distributed. We believe that the greater the extent of the compromised atrial muscle, the higher the probability that paroxysmal atrial fibrillation will develop in patients with sick sinus syndrome.

The interelectrode distance of bipolar catheters, the filter frequency settings,[23] the high gain recordings, and the motion at the electrode-tissue interface[24] may affect the recording of fragmented electrograms by the endocardial mapping technique. We used a catheter with a 10 mm interelectrode distance, which is the standard catheter used by most laboratories. Catheters with such a wide interelectrode distance can record more distant electrical activity. Knowledge of the effect that filter settings have on electrogram duration is not fully complete, but the filter setting is known to influence the amplitude of the electrograms. The narrower the band pass selected, the lower the amplitude of the recorded signal obtained. We measured the duration and the number of fragmented deflections of the electrograms not their amplitude. All the atrial endocardial electrograms in our study were recorded at a fixed gain setting and they remained constant and reproducible at each recording site in individual patients.

Although these fractionated electrograms could be non-specific abnormalities or even artefacts of the recording technique, there is a well established association between their presence and the occurrence of sustained ventricular tachycardia in patients with ischaemic heart disease,[25-27] that arises from areas of asynchronous and slow conducted depolarisations. Furthermore, a prolonged and fractionated atrial electrogram is known to be characteristic of paroxysmal atrial fibrillation that is closely associated with vulnerability of the atrial muscle.[7]

Fragmented electrical activity is often recorded by a local atrial electrogram in response to single premature atrial stimulation in patients with paroxysmal atrial fibrillation.[28-30] Furthermore, fragmented atrial electrograms suggesting areas of abnormal conduction have been recorded within the circuit in human atrial flutter.[31] Recent clinical mapping studies during atrial flutter showed that fragmented electrograms with a double-spike pattern were recorded from the posterior and posterolateral right atrial wall in most patients.[32 33] We studied the atrial electrograms during sinus rhythm by means of an endocardial catheter mapping technique. Thus we recorded fragmented double-spike electrograms in only one patient with sick sinus syndrome. This finding is consistent with that of Olshansky *et al*[33] who performed sequential site atrial mapping during sinus rhythm expressly to search for double potentials in nine patients. They found double potentials only in one patient though all their patients had double-spike electrograms during atrial flutter.

Our results help to elucidate the mechanisms responsible for precipitating paroxysmal atrial fibrillation in patients with sinus node dysfunction. We found that the prolonged and fractionated electrical activity represented anatomic areas of the atrial muscle where reentry was likely. We found that abnormal atrial electrograms were generally localised to the high right atrium in patients with sick sinus syndrome who did not have tachycardia, whereas they were more widely distributed in the right atrium of patients with both sick sinus syndrome and paroxysmal atrial fibrillation. The greater the extent of the compromised atrial muscle the higher the probability that paroxysmal atrial fibrillation will develop in patients with sick sinus syndrome.

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Non-atherosclerotic coronary artery disease and sudden death in the young

Domenico Corrado, Gaetano Thiene, Patrizia Cocco, Carla Frescura

Abstract

***Objective*—To assess prevalence and type of non-atherosclerotic coronary artery disease in young people (≤35 years) who died suddenly.**

***Design*—A necropsy study of 150 consecutive cases of sudden death (that is, within 6 h of the onset of symptoms).**

***Results*—Death was attributed to coronary artery disease in 48 cases: in 16 (33%) of them the disease was non-atherosclerotic. Twelve subjects (eight males and four females, age range 2–35 years, mean 24·2) had congenital anomalies: a deep intramyocardial course in six, origin from the wrong sinus in three, and ostial obstructions in three. Sudden death was the first manifestation of disease in six cases. The other six had a history of palpitation or syncope or both. An electrocardiogram was available in five cases and showed ventricular arrhythmias in four; none had angina pectoris. Stress testing was available in two cases: neither showed any effort-dependent ST-T abnormalities. In six cases sudden death was related to physical exercise. Acquired non-atherosclerotic coronary artery disease was found in four cases: spontaneous coronary dissection in three previously symptom free patients and Kawasaki coronary arteritis in one child who had had acute myocardial infarction.**

***Conclusion*—One third of the cases of fatal coronary artery disease were non-atherosclerotic with coronary artery anomalies being the most frequent form. Coronary artery anomalies should be suspected in young patients who have symptoms of ventricular arrhythmias without any overt signs and symptoms of ischaemia.**

(*Br Heart J* 1992;68:601–7).

Clinical and pathologic studies have shown that atherosclerotic coronary artery disease, often complicated by acute thrombosis, is the most common cause of sudden death in adults.[1-3] The few studies of sudden death in young people showed that in this subgroup ischaemic cardiac arrest was often triggered by non-atherosclerotic coronary artery disease.[4-10] The incidence, clinical significance, mechanism of ischaemia, and possibility of early diagnosis of non-atherosclerotic disease have not been studied, however.

We report here the clinical and pathological findings in a group of young people who died suddenly of non-atherosclerotic coronary artery disease since 1979 in the Veneto region (northeast) of Italy.

Patients and methods

The Veneto region covers an area of 18 368 km.[2] In the 1985 census it had a population of 4 370 533. The residents are white and the population is ethnically homogeneous. Italian law does not require postmortem examination of all persons who die suddenly so fatal cases were reported to pathologists or medical examiners only at the specific request of the General Attorney. All sudden deaths reported during this period were included in this study, but we do not know how many cases were not referred for postmortem examination. After necropsy the hearts were forwarded to the Institute of Pathological Anatomy of the University of Padua for detailed morphological study.

From 1 January 1979 to 30 September 1991 we collected 150 consecutive cases of juvenile sudden death, which was defined as an unexpected natural fatal outcome within 6 h of the initial symptoms in people aged 35 or less; cases of infant sudden death syndrome were excluded. The methods of investigation have been reported in detail elsewhere.[8 9 11]

There were 126 sudden fatal cardiovascular events and death was attributed to coronary artery disease in 48 cases: 32 had obstructive atherosclerotic coronary artery disease and 16 (33%) had non-atherosclerotic coronary artery disease.

Sudden death was deemed to be coronary in origin in the absence of other cardiac pathology and in the presence of ischaemic damage in the myocardial territory supplied by the affected coronary artery.

Results

The table shows the main clinical and pathological findings.

Twelve individuals (8 male and 4 female, aged 2–35 years (mean 21·6) had congenital coronary anomalies. In six the fatal event occurred at rest and in six it was related to physical exercise (during effort in five and after effort in one). In six sudden death was the first manifestation of the disease. The other six had a history of palpitation or syncope or both; a resting electrocardiogram was available in five and had showed isolated ventricular extrasystoles in four (fig 1A and B). Ambulatory Holter monitoring was available in two. It showed complex ventricular arrhythmias consisting of ventricular couplets in patient 5 and non-sus-

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Sudden death in the young caused by non-atherosclerotic coronary artery disease: main clinical and pathologic findings in 16 subjects

Case No	*Age, sex*	*History*	*Previous ECG findings*	*Circumstances of death*	*Main pathological findings*
			Congenital coronary anomalies		
1	22, M	Athlete, palpitation	Ventricular extrasystoles	During effort	RCA from left coronary sinus
2	29, M	Athlete, palpitation	Ventricular extrasystoles, normal stress testing	During effort	RCA from left coronary sinus. Healed myocardial infarction
3	11, F	Symptom free	Not performed	During effort	LCA from right coronary sinus
4	19, F	Family history of sudden death; symptom free	Normal standard ECG	During sleep	Intramyocardial course of LAD
5	30, F	Palpitation	Multiform extrasystoles, ventricular couplets	At rest	Intramyocardial course of LAD
6	27, M	Symptom free	Not performed	At rest	Intramyocardial course of LAD
7	35, M	Symptom free	Not performed	During effort	Intramyocardial course of LAD
8	14, M	Athlete, effort-induced syncope	Ventricular extrasystoles and unsustained ventricular tachycardia, normal stress testing	During effort	Intramyocardial course of left intermediate coronary artery
9	29, M	Symptom free	Not performed	At rest	Intramyocardial course of LAD
10	2, M	Recurrent syncope	Not performed	After meal	Slit-like lumen of left coronary ostium
11	7, F	Recurrent syncope	Normal standard ECG	After effort	Valve-like ridge of right coronary ostium
12	35, M	Symptom free	Not performed	After meal	Valve-like ridge of right coronary ostium
			Acquired non-atherosclerotic coronary artery disease		
13	34, F	Asymptomatic	Not performed	During sleep	Spontaneous LAD dissection
14	28, F	Pregnancy, Marfan; symptom free	Not available	At rest	Spontaneous LM dissection
15	23, M	Symptom free	Not performed	At rest	Spontaneous LAD dissection
16	6, M	Previous myocardial infarction	Not available	At rest	Kawasaki coronary arteritis

RCA, right coronary artery; LAD, left anterior descending coronary artery; LM, left main coronary artery.

tained ventricular tachycardia in patient 8, in whom neither conduction disturbances nor ventricular tachycardia had been induced during electrophysiological study with programmed ventricular stimulation.

No patient had angina pectoris, and electrocardiographic stress testing in two patients (cases 2 and 8) had not shown any effort-dependent ST-T abnormalities.

Postmortem examination in six cases showed that a subepicardial coronary artery (the proximal tract of the left anterior descending branch in five (fig 2) and the intermediate branch of the left coronary artery in one (fig 3)) followed a deep intramyocardial course. The length of the intramyocardial course ranged from 10 to 25 mm and the depth from 4 to 8 mm. Histological examination showed that the intramyocardial coronary segments were separated from the subepicardial fat by a myocardial bridge and were also encircled by a muscular "sheath" that compressed and deformed the coronary lumen; moreover, we found myocardial disarray around the intramural segment in four cases (fig 4). In every case the myocardial tributary of the intramural coronary artery showed histological features of ischaemic injury, consisting of an acute myocardial infarction of the left ventricular lateral wall (case 8) (fig 3B), a post-infarction scar in the interventricular septum (case 5), and signs of "hyperacute" myocardial damage such as contraction band necrosis (fig 2B) and wavy fibres in the anteroseptal wall of the left ventricle in the four other cases.

A coronary artery originated from the wrong aortic coronary sinus in three cases. In two (cases 1 and 2) both the right and left coronary arteries arose from the left coronary sinus (fig 1C) and the proximal tract of the right coronary artery ran between the aorta and the pulmonary infundibulum, following an intramural course in the aortic tunica media and with a slit-like lumen. We found scattered foci of contraction band necrosis in the posteroseptal wall of the left ventricle in both cases and an extensive healed posterior myocardial infarction in one (case 2). In case 3 the left coronary artery had an anomalous origin from the right coronary sinus and ran between the aorta and pulmonary artery and partially within the wall of the aorta (fig 5); a large anterior subacute myocardial infarction was also seen.

Isolated malformations that obstructed the ostial lumen were found in three cases. In two (cases 11 and 12) the right ostium was obstructed by a valve-like ridge produced by a fold in the elastic tunica media of the aorta (fig 6). In the third (case 10) the left coronary ostium had a slit-like lumen caused by stenosis (fig 7).

There was evidence of acquired non-atherosclerotic coronary artery disease in four cases (two male and two female, aged 6–34 years (mean 22·7 years)). In three previously symptom free subjects sudden death was caused by spontaneous coronary dissection: in one patient (case 14) with Marfan's syndrome who was pregnant, the left main stem was affected. In the other two (cases 13 and 15), who had no risk factors, the dissection affected the left descending coronary artery. Cystic medial necrosis was seen only in the case with Marfan's syndrome.

Case 16 died suddenly three years after a myocardial infarction. The postmortem examination showed Kawasaki coronary arteritis causing aneurysms and thrombosis of all the proximal subepicardial coronary arterial trunks, leading to severe ischaemic cardiomyopathy.

Discussion

Postmortem examinations after sudden cardiac death in adults,[12 13] and coronary arteriography studies in survivors of cardiac arrest generally showed extensive coronary atherosclerosis.[1 2] Unlike these older populations, 33% of cases of fatal coronary artery disease in our juvenile series were caused by non-atherosclerotic dis-

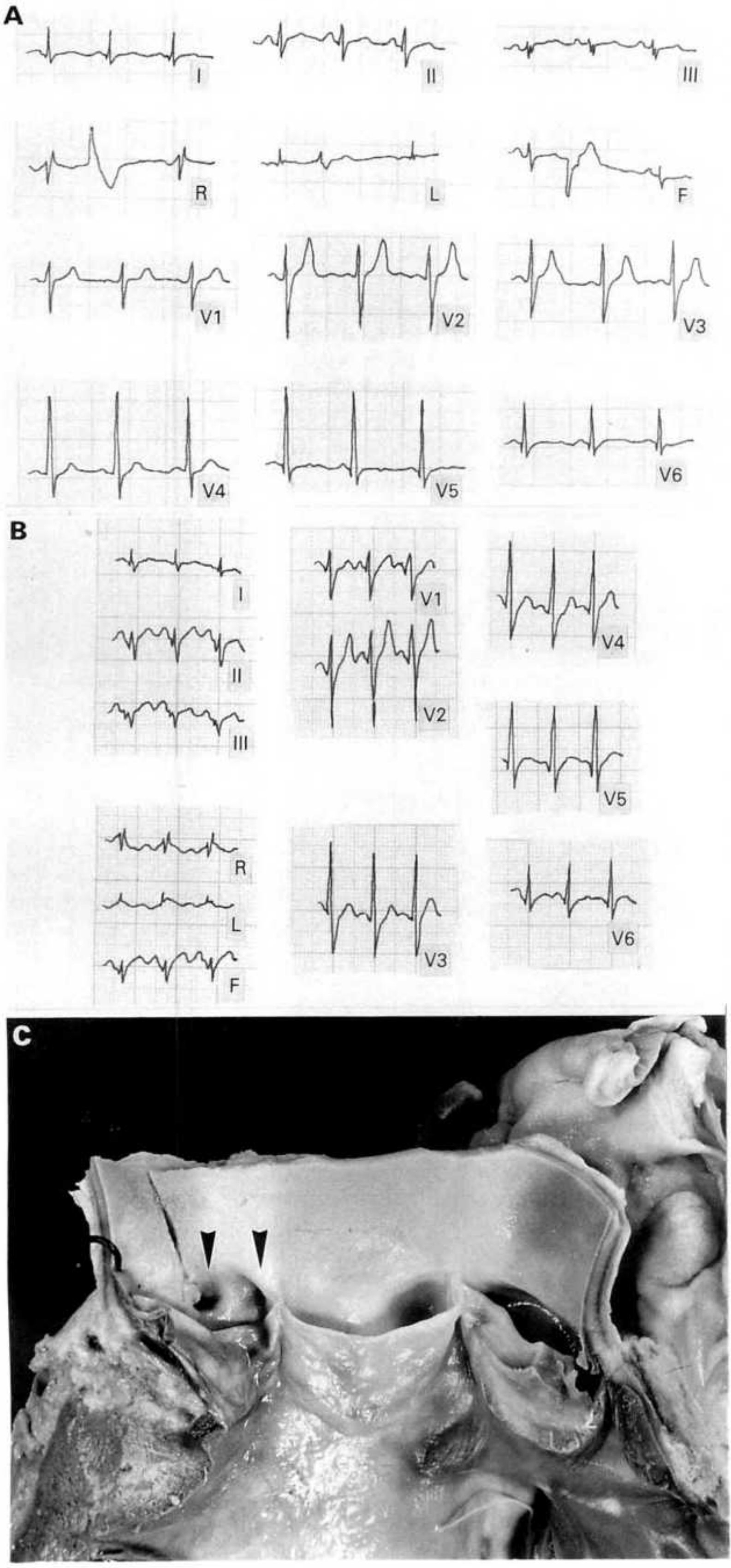

Figure 1 Electrocardiograms (ECG) and cardiac morphology in a 29 year old male athlete (case 2) who died suddenly during effort. (A) Resting ECG showing isolated ventricular extrasystoles. (B) The ECG during effort did not show any ischaemic ST-T changes or arrhythmias. (C) Gross view of the aortic root showing that both coronary ostia originated from the left coronary sinus (arrows).

ease—chiefly congenital anomalies in the origin and course of coronary arteries, which were found in about 10% of all cases of cardiovascular sudden death. This finding accords with previous studies that identified congenital coronary artery disease as the cause of 5–35% of the cases of sudden cardiac death in young people.[4-7] However, in contrast to previously published series in which the most common coronary anomaly was an origin from the "wrong" coronary sinus, we found a wider range of abnormalities including coronary ostial malformations and the coronary trunks following an intramyocardial course. This latter condition has long been regarded as a normal anatomical variant[14 15]; however, recent clinical and pathological studies showed that myocardial bridging of the coronary arteries can lead to myocardial ischaemia manifested as angina,[16-18] myocardial infarction,[18-20] and sudden death.[21] Faruqhi *et al* reported a significant clinical improvement in ischaemic symptoms after surgical debridging of the coronary artery.[18]

The role of intramyocardial coronary arteries in precipitating fatal myocardial ischaemia during strenuous exercise was confirmed by Morales *et al* in a pathological study. They found ischaemic damage at various stages of healing in the myocardial territory supplied by the intramural coronary artery.[21] Nonetheless, the pathophysiology of myocardial ischaemia caused by gross epicardial coronary trunks taking an intramyocardial course is still unknown. Effort-induced ischaemia has been attributed to tachycardia which increases the myocardial oxygen requirement and reduces the coronary flow during diastole.[18] Ischaemia at rest, however, could be caused by vasospasm in the intramural coronary segment[22-25] and the transient formation of platelet aggregates[20] and/or thrombosis[19] provoked by mechanical trauma of the vessel wall. The importance of myocardial bridging in patients who died suddenly is uncertain because this feature is not uncommon in healthy individuals. Ferreira *et al* examined a series of hearts at necropsy.[26] They found that myocardial bridging was common but that only a deep and long intramyocardial course caused myocardial ischaemia. We too found that when a coronary artery followed a particularly deep and long intramyocardial course it could cause ischaemic cardiac arrest. We often found signs of hyperacute, recent or healed ischaemic injury in the myocardial territory supplied by a tributary of the intramural coronary artery. Case 14 is paradigmatic in that, to the best of our knowledge, it is the first reported necropsy case of effort-induced regional acute myocardial infarction with a corresponding intramural coronary arterial trunk.

Where a coronary artery followed a long and deep intramyocardial course we found the distinctive histological feature of ventricular myocardium organised to form a "sheath" encircling the intramural coronary segment with myocardial disarray and fibrosis. Could this myocardial ring have caused paroxysmal obstruction of the intramural coronary segment by inducing "extrinsic" prolonged constriction? At angiography this mechanism can be indistinguishable from an "intrinsic" coronary vasospasm.[22-25] Alternatively, the myocardial disarray and fibrosis surrounding the

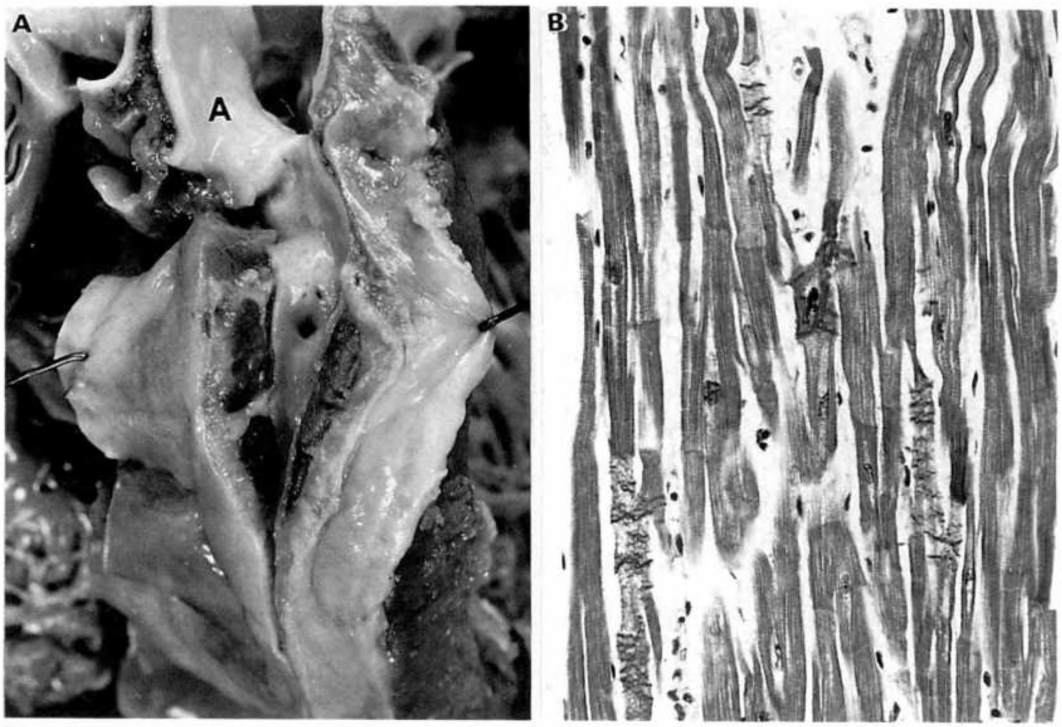

Figure 2 Cardiac morphology and histology in a 35 year old man (case 7) who died suddenly during exercise. (A) Gross view of the deep and long intramyocardial course of the left anterior descending coronary artery. (B) Contraction band necrosis in myocardium supplied by the tributary vessel. (Azan stain; original magnification, × 480. A, aorta).

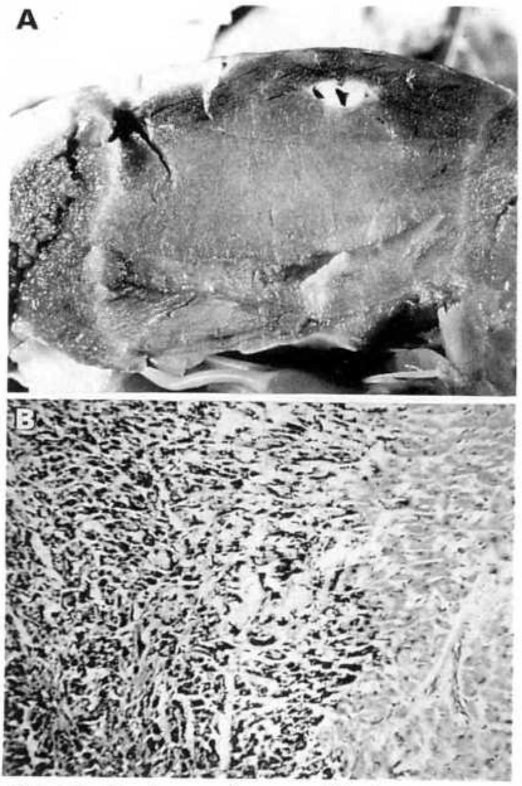

Figure 3 Cardiac morphology and histology in a 14 year old boy who died suddenly during a soccer game (case 8). (A) Gross view of the lateral left ventricular free wall showing a deep intramyocardial course of the intermediate branch of the left coronary artery. (B) Massive necrosis in the tributary myocardium. (Acid phosphotungstic stain; original magnification, × 75).

intramural vessel might have acted as a "restrictive" perivascular tissue to limit the diastolic flow in the coronary segment.

Case 14 had complained of syncope and had electrocardiographic evidence of ventricular arrhythmias but did not show any ST-T abnormalities in a maximal exercise test. A non-diagnostic electrocardiographic stress test was also obtained in one patient (case 2) who had an anomalous origin of the right coronary artery from the left coronary sinus and isolated extrasystoles on a resting electrocardiogram. Others have attributed fatal myocardial ischaemia in such cases to aortic root expansion, which increases the acute angulation of the coronary take-off, and compresses the vessel against the pulmonary trunk.[27–30] Our histological findings suggest that the intramural course of the anomalous coronary artery in the aortic tunica media may be crucial because it produces a slit-like lumen.[31] Thus in the absence of a fixed atherosclerotic coronary obstruction, the pathophysiological determinants of myocardial ischaemia are not readily reproducible, and this hinders the diagnosis of these congenital coronary anomalies that predispose to life-threatening arrhythmias.

None of our patients had had typical angina attacks and in half of them sudden death was the first manifestation of the coronary anomaly. Prodromal symptoms in the remaining subjects consisted of palpitation or syncopal episodes or both; electrocardiograms, when available, generally showed ventricular arrhythmias, such as isolated extrasystoles and unsustained ventricular tachycardia, in the absence of ST-T abnormalities. Therefore, in young patients with alarming symptoms of ventricular arrhythmia, an "ischaemic substrate" should be suspected even if exercise testing is normal and there is no chest pain. The origin and course of the coronary arteries should be investigated by a detailed echocardiographic study of the aortic root and, in selected cases, by coronary angiography.[30 32 33]

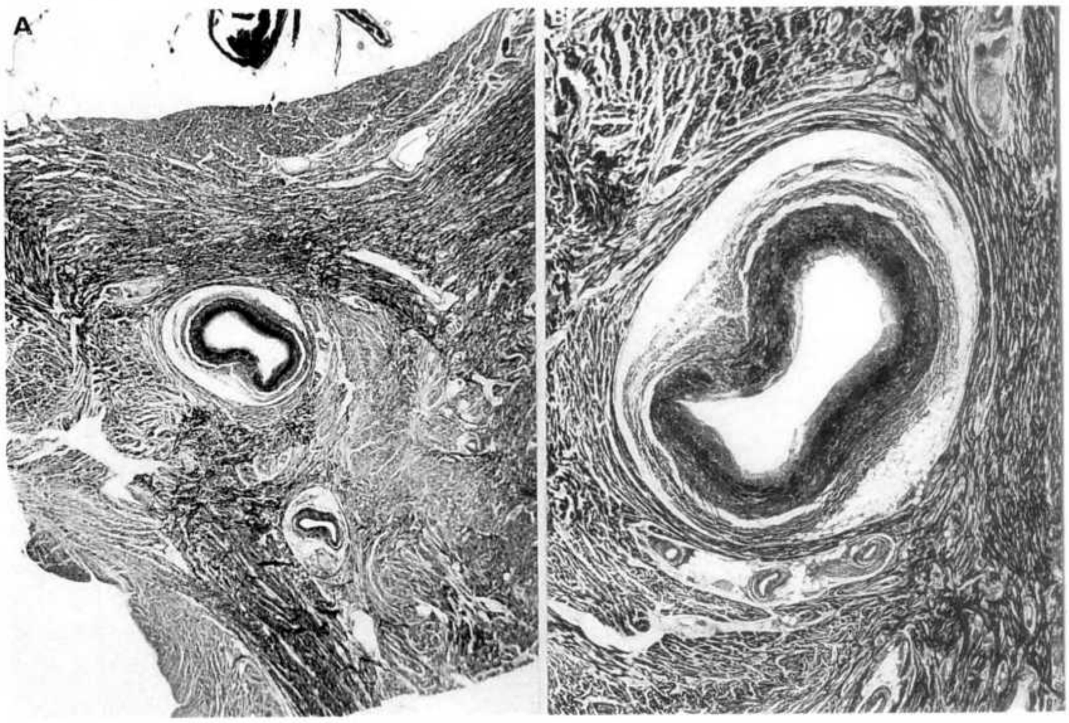

Figure 4 Histological examination of the heart of a 29 year old man who died suddenly at rest (case 9). (A) The anterior interventricular groove showing the intramyocardial course of the left anterior descending coronary artery. (Azan stain, original magnification, ×8). (B) Increased magnification of (A) (×18) showing the myocardial sheath encircling the coronary segment and dysplasia of the myocardium producing disarray.

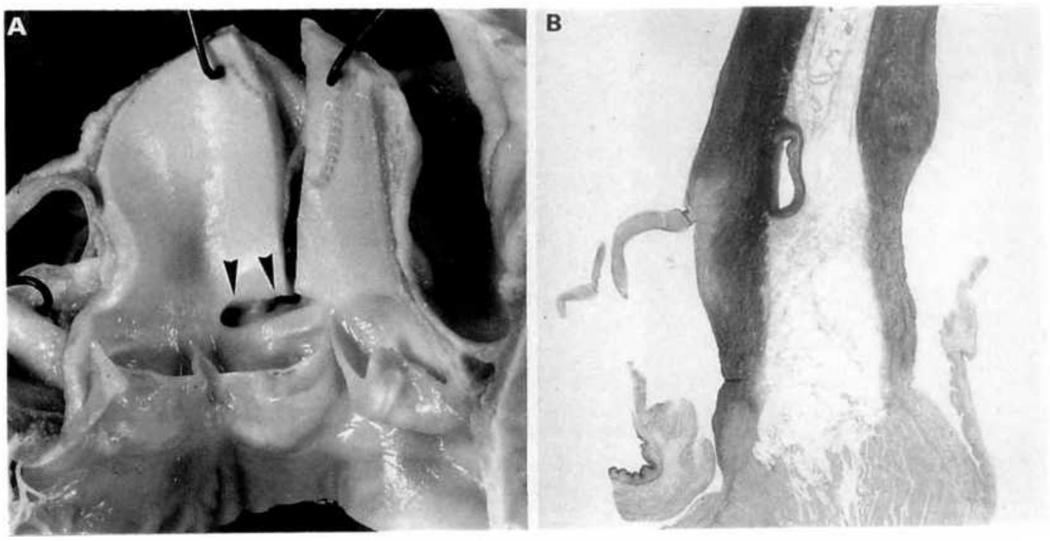

Figure 5 Cardiac morphology and histology in an 11 year old girl who died suddenly during effort (case 3). (A) Gross view of the aortic root showing that both coronary ostia arise from the right coronary sinus (arrows). (B) Histological examination of the first segment of the left coronary artery showed that it ran in between the aorta and pulmonary artery. (Weigert-van Gieson, original magnification, ×6).

Congenital malformations of the coronary ostium such as a valve-like ridge or slit shaped lumen, that cause ostial stenosis, have been found only at necropsy, usually in association with anomalous origin of the coronary artery from the wrong coronary sinus[34] or in combination with severe atherosclerotic coronary artery disease.[35] In our cases, however, the malformation was isolated and was also seen in children. Virmani *et al* postulated that ostial valve-like ridges may act as occlusion valves in the ostium, and thus predispose to sudden myocardial ischaemia.[35] In our cases the fatal event occurred after eating (cases 10 and 11) or after effort (case 11), when a transient neurovagally mediated episode of hypotension could have been responsible for a sudden drop in aortic pressure, thus compromising the perfusion of the narrowed coronary ostium. Case 10 had had previous syncopal episodes that were interpreted as epileptic attacks.

The most common acquired non-atherosclerotic coronary artery disease in our series was spontaneous coronary artery dissection. This condition is usually an unrecognised cause of acute myocardial infarction or sudden death in young patients, especially peripartum women.[36–40] Its aetiology is uncertain. Coronary artery dissection was idiopathic in two of our cases and related to pregnancy in

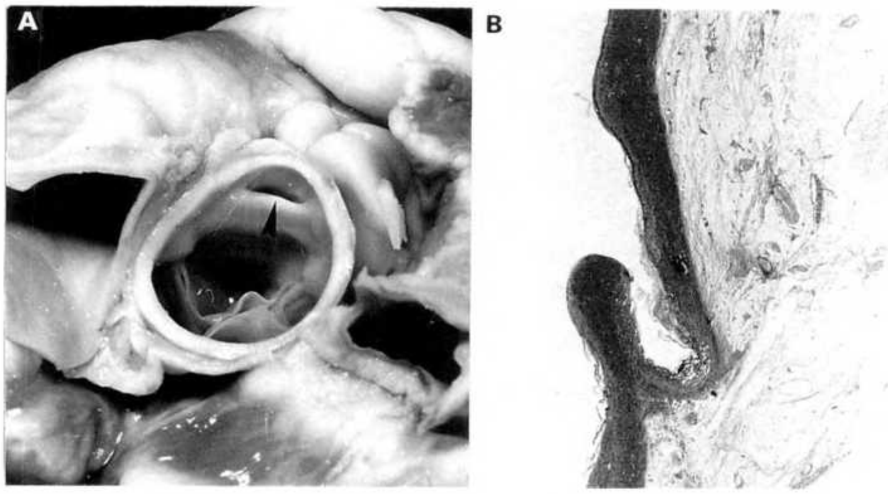

Figure 6 Cardiac morphology and histology in a 7 year old girl who died suddenly after effort (case 7). (A) A valve-like ridge (arrow) obscured the right coronary ostium. (B) Histological examination showed that the ridge was an aortic wall plication. (Weigert-van Gieson, original magnification, × 8).

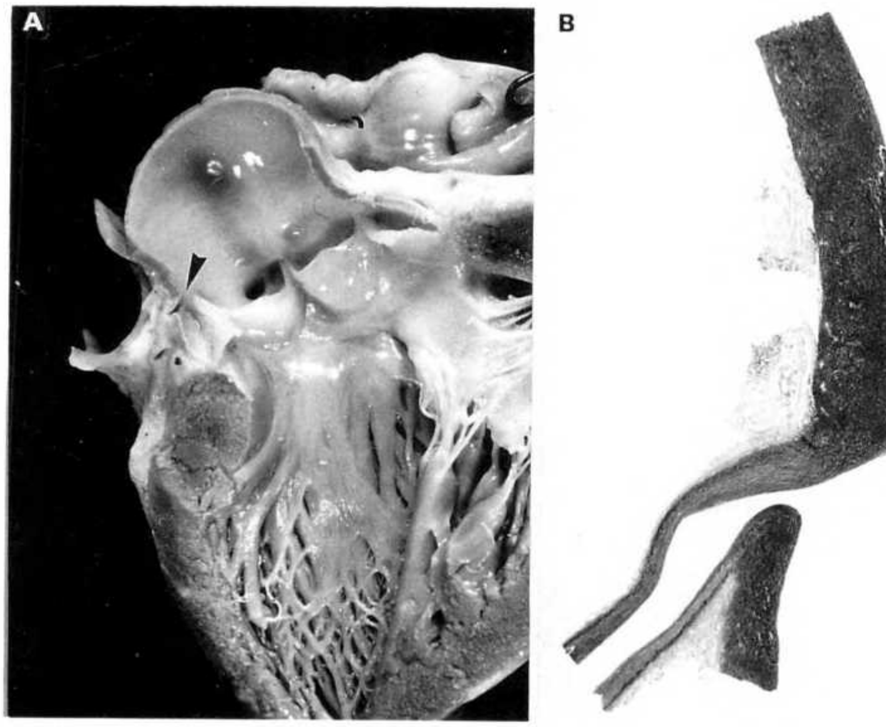

Figure 7 Cardiac morphology and histology in a 2 year old child who died suddenly soon after eating (case 10). (A) Gross view of the left ventricular outflow tract showing the slit-like left coronary ostium (arrow). (B) Histological examination showing a narrowing of the coronary ostium (compare with the diameter of the main left coronary trunk). (Weigert-van Gieson; original magnification, × 8).

the patient with Marfan's syndrome who died suddenly during the third trimester.

This study suggests that non-atherosclerotic coronary artery disease is an important cause of fatal cardiac arrest in the young. It was present in one third of the cases of juvenile sudden coronary death that we studied. Congenital coronary diseases, consisting of apparent minor abnormalities of the ostium and of the origin and course of the coronary arteries, were the most frequent form of non-atherosclerotic coronary artery disease and were responsible for nearly 10% of juvenile sudden cardiac deaths in our series of necropsy cases. Angina or ischaemic electrocardiographic patterns were never seen, whereas half these cases had had arrhythmic symptoms (palpitation or syncope or both) and electrocardiographic signs (ventricular arrhythmias).

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Addendum

Since the submission of the paper, we have studied 23 additional cases of juvenile sudden death. We found evidence of non-atherosclerotic coronary artery disease in two of them. An 11 year old boy who died suddenly while playing soccer had an anomalous origin of the left coronary artery from the right aortic coronary sinus. A 14 year old girl who died suddenly at school had Takayasu arteritis that also affected the coronary ostia.

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Br Heart J 1992;68:608–12

MEASUREMENT

Adjustment for the influence of age and heart rate on Doppler measurements of left ventricular filling

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Abstract

***Objective*—To determine the normal range of pulsed Doppler measurements of left ventricular filling adjusted for age and heart rate.**

***Design*—Multiple regression was used to measure the effects of age and heart rate on pulsed Doppler indices of left ventricular filling in normal subjects. These regression equations were used to calculate a predicted normal value and 95% confidence interval (95% CI) for any subject from his age and heart rate.**

***Participants*—61 subjects with no evidence of cardiovascular disease, aged 20 to 90 years, with a resting heart rate of 47–89 beats/min.**

***Results*—The effect of a 10 year increase in age was peak atrial filling velocity +15% (95% CI 12·0% to 18·5%); peak early filling velocity −3·2% (−6·0% to 0%); isovolumic relaxation time +6·2% (3·9% to 8·4%); acceleration time −3·8% (−6·0% to −1·5%); deceleration time +7·9% (5·1% to 10·8%). The effect of a 10 beat/min increase in heart rate was: peak atrial filling velocity +5·5% (1·2% to 10·1%); peak early filling velocity −4·0% (−8·1% to 2·0%); isovolumic relaxation time −2·5% (−4·6% to 0·6%); acceleration time −3·1% (−6·4% to 0·4%); deceleration time −1·8% (−4·0% to 3·8%).**

***Conclusion*—For any individual, comparison of the predicted normal measurement and 95% CI with the observed measurement allows an assessment of the effects of disease on left ventricular filling that is independent of age and heart rate.**

(*Br Heart J* 1992;68:608–12)

Doppler ultrasound is a non-invasive tool that is potentially useful for assessing left ventricular diastolic function. Changes in left ventricular diastolic filling have been measured in a wide range of cardiovascular conditions.[1-3] A major problem, however, is that measurements of filling vary in normal subjects with both age[4-8] and heart rate[9-11] making interpretation of disease related changes more difficult. The changes reported with normal aging are similar to changes reported with hypertension, ischaemia, and hypertrophy.[1 2] Most studies have used a control group of similar age and heart rate or both when assessing changes with disease. This does not, however, allow an assessment of diastolic filling in individual patients that is independent of age and heart rate.

A method of adjusting for the influence of age and heart rate on Doppler indices of left ventricular filling is proposed.

Patients and methods

PATIENT SELECTION

Subjects had no evidence of cardiovascular disease in their history, physical examination, or cross sectional echocardiography, they were taking no medication for cardiovascular disease, and there was no evidence of infection, thyroid disease, or metabolic disturbance. All subjects older than 35 years had a normal electrocardiogram, chest *x* ray film, urea and electrolytes, and haemoglobin. Most subjects were healthy volunteers or patients admitted to hospital for minor surgical procedures. Five subjects were excluded because Doppler studies were of poor quality. All subjects gave informed consent.

Sixty one subjects were included in the study. The mean age was 53 (SD 20·4, range 20 to 90) years. The mean heart rate was 68 (SD 11, range 47 to 89) beats/min.

CROSS SECTIONAL ECHOCARDIOGRAPHY AND DOPPLER STUDIES

Cross sectional echocardiographic and Doppler studies were performed with the Toshiba 65A imaging system. Pulsed Doppler recordings of left ventricular filling velocities were obtained from the apical four chamber view with a 2·5 MHz transducer. The sample volume was positioned just proximal to the mitral leaflet tips with alignment adjusted to optimise the recording of flow velocity and to minimise the angle between the blood flow vector and the ultrasound beam. The flow velocity curves were recorded on videotape at 50 mm/s. Measurements were performed at a later time by an observer blind to the patient's age.

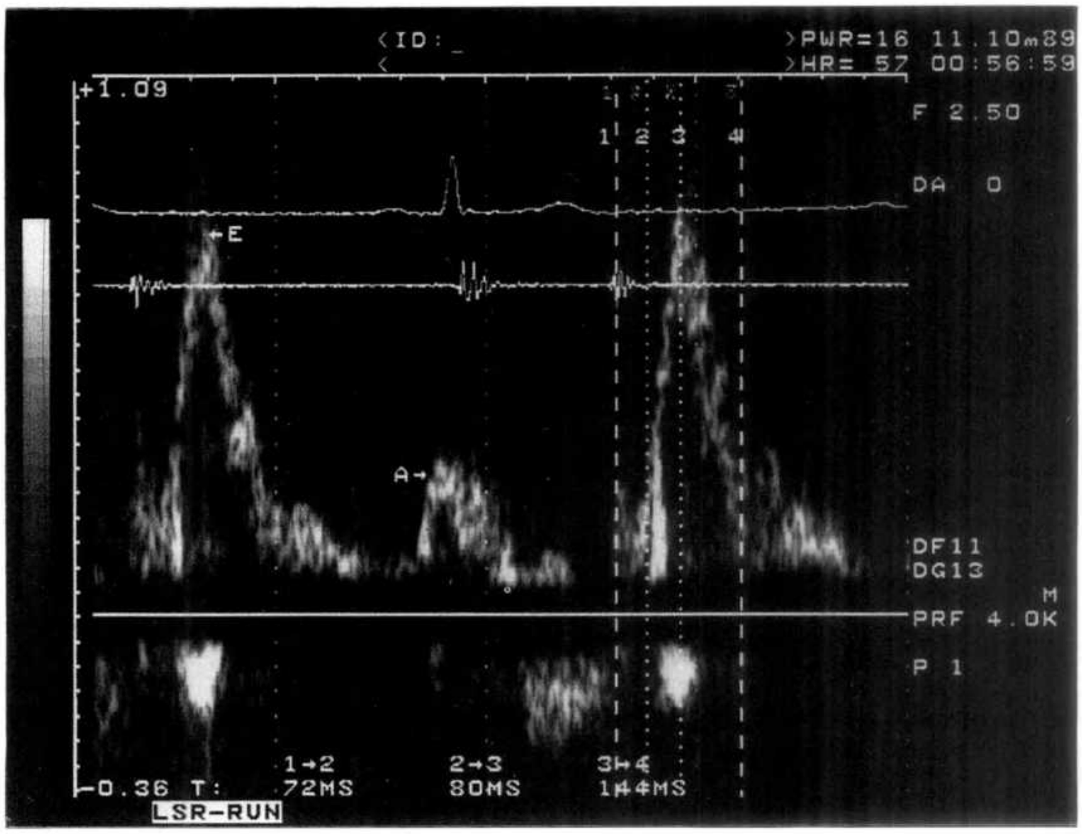

Figure 1 Measurements made from the left ventricular filling waves: peak early diastolic filling velocity (E); peak atrial filling velocity (A); isovolumic relaxation time (1–2); acceleration time (2–3); deceleration time (3–4).

MEASUREMENTS OF THE LEFT VENTRICULAR FILLING WAVES

Doppler measurements were made from three to five cycles with the most clearly defined velocity wave form and the average of measurements used. The measurements made were: peak velocity of the early diastolic filling wave, E; peak velocity during the atrial contribution to filling, A; isovolumic relaxation time; the time from the start of filling to E (the acceleration time); and the time from E to the end of the early filling wave F (deceleration time). The isovolumic relaxation time was measured from the earliest point of the deflection that occurs immediately after the completion of left ventricular ejection, to the start of left ventricular filling. In 12 patients this time was mean (SD) 5 (7) ms longer than the time from the greatest deflection of the aortic closure sound recorded by phonocardiograph to the start of filling. For E, F, and A, the midpoint of the Doppler velocity recording was measured. If the early and late filling waves overlapped, or if there was wide spectral spread during the last part of the early filling wave, the F point was determined by extrapolating the downslope of the early filling wave onto the baseline (fig 1).

ANALYSIS AND STATISTICS

Each filling measurement was regressed on age and heart rate by multiple linear regression. The natural logarithm (ln) of each measurement was also regressed on age and heart rate to determine whether proportional changes better fitted the regression model. Proportional changes are expressed in percentages.

To determine whether the effect of age is influenced by the heart rate, or vice versa, a term for interaction was included in the regression equations. The regression coefficient for this term was not significant ($p > 0{\cdot}1$) for any of the measurements, so this term was dropped.

The size and direction of the change in a diastolic measurement with change in age or heart rate is given by the slope of the regression line and r^2, which measures the proportion of the variance explained by the regression. The 95% confidence interval (95% CI) for the slope is quoted.

The predicted normal measurement can be calculated from the patient's age and heart rate in the appropriate regression equation. For each patient, the error in the prediction is the difference between the observed and the predicted values. The normal range is the range in which 95% of normal people would be predicted to lie, and was estimated as the predicted measurement within 2 SDs of this error. This simplied method of estimating the normal range is approximate. It does not take into account the increase in the width of the normal range with values of age and heart rate that are further from the mean values for the group from which the regression equations were calculated.

The normal range was also calculated by the standard method[12] to see if the approximate but simplified method gives acceptably close results. The difference in the size of the normal range calculated with the two methods was determined for ages from 20 to 80 and heart rates from 50 to 85. The greatest difference is given as a percentage and is the same for all indices.

Estimation of the normal range assumes that the spread of the real values about the regression line is constant throughout the range of ages and heart rates. This assumption was

Table 1 Comparison of the adequacy of the regression model with absolute measurements and the natural logarithm of diastolic measurements

	Proportion of variation (%) explained by differences in age and heart rate (r^2)		*Non-constant variance, p value*	
Diastolic measurement	*Absolute*	*Logarithm*	*Absolute*	*Logarithm*
Isovolumic relaxation time	36	36	<0·0001	0·21
Acceleration time	18	22	0·49	0·007
Deceleration time	40	37	<0·0001	0·072
Peak early filling velocity, E	11	16	0·0003	0·0017
Peak atrial filling velocity, A	69	69	<0·0001	0·98
A/E	71	77	0·072	0·48

tested by a variant of Anscombe's test for non-constant variance in regression.[12]

Results

COMPARISON OF LINEAR AND PROPORTIONAL MODELS

A similar proportion of the total variance is explained by simple regression and regression of the natural logarithm of each index for age and heart rate (table 1). The peak filling velocity during the atrial contribution (A) and A/E had the strongest association with age and heart rate, and the acceleration time and peak early diastolic filling rate had the weakest.

For the peak atrial filling velocity, the deceleration time, the isovolumic relaxation time, and A/E the spread of values above and below the regression line increased as the predicted measurement increased. For these indices this trend for increasing spread was not significant ($p > 0·05$) if the natural logarithm was used. Conversely, for the acceleration time and peak early filling velocity the spread of values tended to decrease as the predicted value increased and this trend was not improved by taking logarithms (table 1).

Figure 2 illustrates this correlation for A, E, and the logarithm of A and E.

CALCULATION OF THE NORMAL RANGE

To calculate the normal range by the simple method, the predicted measurement is multiplied by the values given in table 2. The normal range is skewed because it is calculated from logarithms. The greatest increase in the size of the normal range calculated by the standard method compared with the simplified method was 5·6% at age 20, heart rate 85.

SIZE OF AGE AND HEART RATE EFFECTS

Table 3 summarises the effect of increasing age by 10 years and increasing heart rate by 10 beats/min in each of the diastolic measurements. The effect of age was significant for all indices ($p < 0·05$) but the effect of heart rate

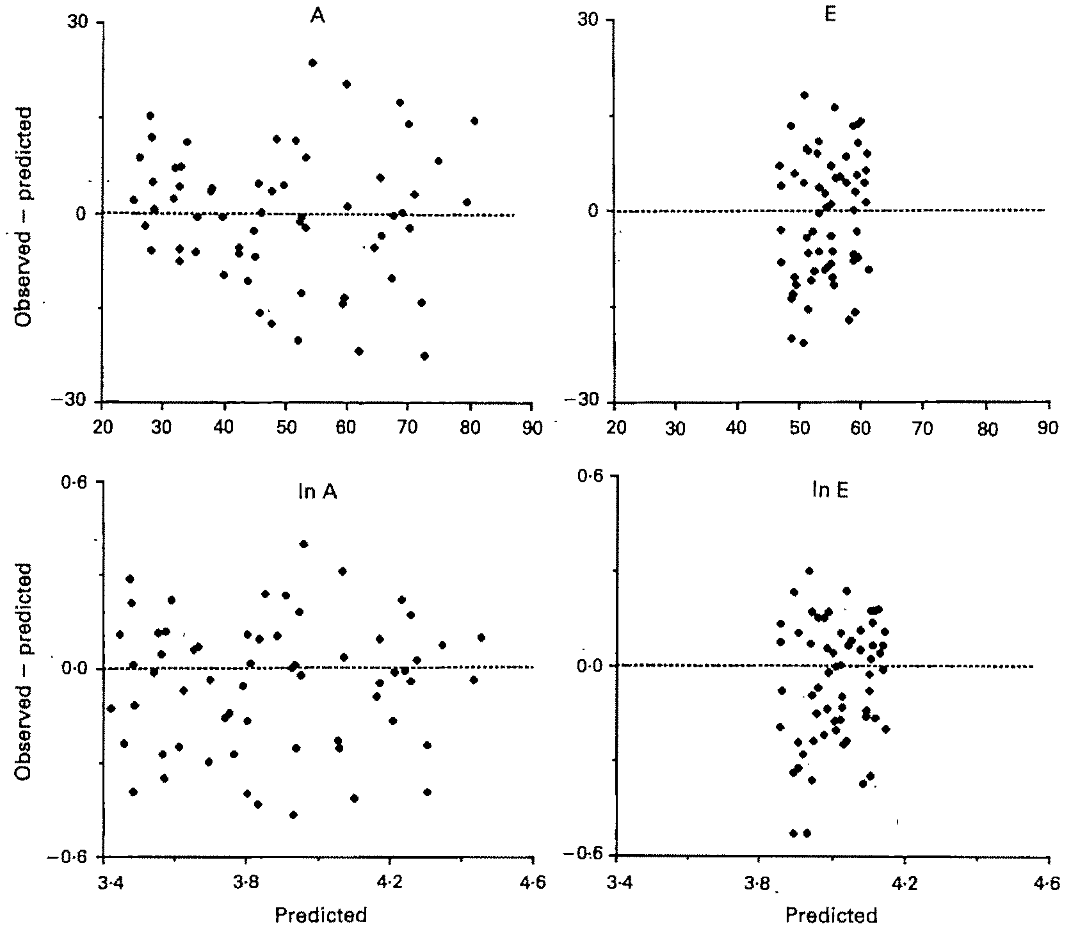

Figure 2 For the peak atrial filling velocity (A, measured in cm/s), the difference between the observed and the predicted measurements increases as the predicted measurement increases. For the natural logarithm of A (ln A) the difference between the observed and predicted measurements remains constant throughout the range of ln A. The peak early diastolic filling velocity E varies over a narrower range than A. A trend for the difference between the observed and predicted values of E to decrease as E decreases is aggravated by taking logarithms (ln E).

Table 2 Mean (SD) and normal range of diastolic indices.

Diastolic measurement	*Observed measurements (mean (SD))*	*95% CI of normal values about the predicted value (z)*
Isovolumic relaxation time (ms)	67 (14)	0·73z to 1·43z
Acceleration time (ms)	78 (14)	0·70z to 1·42z
Deceleration time (ms)	166 (42)	0·68z to 1·48z
Peak filling rate (cm/s)	57 (13)	0·66z to 1·51z
Peak atrial filling rate (cm/s)	51 (19)	0·68z to 1·47z
A/E	0·95 (0·42)	0·66z to 1·54z

The normal range can be estimated with the approximate method by multiplying the predicted measurement (z) by the constants in the second column.

was only significant for A and A/E. Figure 3 shows the variation of ln A with age and heart rate.

Table 4 gives the equations for the regression of the logarithm of each diastolic index incorporating age and heart rate.

EXAMPLE OF ADJUSTMENT FOR AGE AND HEART RATE

A patient with left ventricular hypertrophy is 50 years old, and the heart rate is 80 beats/min. A is 90 cm/s. The predicted normal measurement for ln A is calculated with the equations in table 4:

$\ln A = 2{\cdot}77 + (0{\cdot}0142 \times 50) + (0{\cdot}0054 \times 80) = 3{\cdot}91.$

The predicted normal measurement for A is the exponential of 3·91 = 50 cm/s and the 95% CI is between 34 cm/s and 73 cm/s (table 2). The result can also be expressed as a percentage of the predicted normal mean. In this case A is 180% of the predicted mean for normal subjects, with 95% of normal subjects falling within the range 68% to 147%.

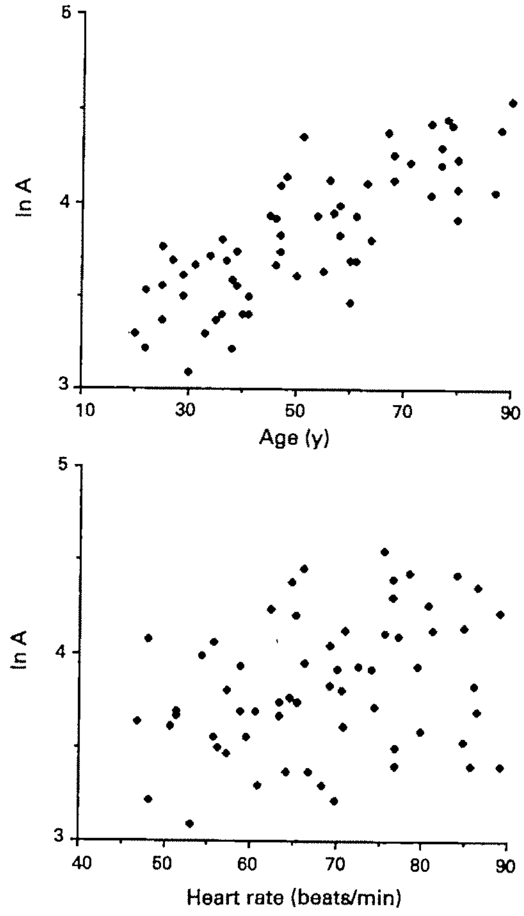

Figure 3 Relation between the natural logarithm of the peak atrial filling velocity (ln A), and age and heart rate. Ln A varies more closely with age than with heart rate.

Discussion

With multiple regression it is possible to measure the effects of age and heart rate on left ventricular filling simultaneously and to adjust for these effects. This makes it much easier to measure the size of the effect of disease in individual subjects.

Linear regression assumes a linear relation between variables and constant variance about the regression line. For the isovolumic relaxation time, the deceleration time, and the peak atrial filling velocity, the spread of observed values increased with the size of the predicted measurement. Therefore estimation of the size of the normal range is inaccurate, as it is too large for small values and too small for large values. This problem was overcome by a logarithmic transformation that measures proportional rather than absolute changes. For the peak early filling velocity and the deceleration time non-constant variance was not improved by taking logarithms, so estimation of the normal range is less accurate. These indices were, however, much less influenced by age and heart rate, so correction for their effects may be less important.

Age had a greater effect on diastolic measurements than heart rate, and the only heat rate effect that was significant ($p < 0{\cdot}05$) was on the peak atrial filling velocity. Therefore it may be reasonable to drop the heart rate correction for other indices. The relation between heart rate and left ventricular filling may change at high heart rates when the filling time is limited. In our study no subjects had a heart rate above 90 and it may be inappropriate to use the same adjustment for measurements recorded at higher heart rates. Overlap of filling waves may also influence measurements, and at present there are no clear guidelines on how to

Table 3 Influence of age and heart rate on measurements of left ventricular filling in normal subjects

	Age		*Heart rate*	
Diastolic measurement	*Increase (%)/ 10 years*	*95% CI (%)*	*Increase (%)/ (10 beats/min)*	*95% CI (%)*
Isovolumic relaxation time	6·2*	*3·9, 8·4*	−2·5	*−4·6, 0·6*
Acceleration time	−3·8*	*−6·0, −1·5*	−3·1	*−6·4, 0·4*
Deceleration time	7·9*	*5·1, 10·8*	−1·8	*−4·0, 3·8*
Peak early filling velocity	−3·2*	*−6·0, 0·0*	−4·0	*−8·1, 2·0*
Peak atrial filling velocity	15·0*	*12·0, 18·5*	5·5*	*1·2, 10·1*
A/E	19·1*	*15·8, 22·5*	9·9*	*4·5, 15·6*

Results are based on the regression of the natural logarithm of each index on age and heart rate. *$p < 0{\cdot}05$.

Table 4 Equations for calculating the predicted normal value of each diastolic index from the subjects age and heart rate

ln index	*a*	*b1* *(× age (y))*	*b2* *(× heart rate (beats/min))*
ln IVRT	4·05	0·006	−0·0026
ln acceleration time	4·75	−0·0039	−0·0031
ln deceleration time	4·69	0·0076	−0·002
ln E	4·47	−0·0033	−0·0042
ln A	2·77	0·0142	0·0054
ln A/E	−1·7	0·0175	0·0095

Equations for regression of the natural logarithm (ln) of diastolic indices on age and heart rate. ln (index) = a + b1 (age) + b2 (heart rate). IVRT, isovolumic relaxation time, E, peak filling rate; A, peak atrial filling rate; ln, natural logarithm.

adjust for this. Measuring the effect of between subject differences in heart rate during a standard Doppler study has some advantages over measuring the effects of interventions such as atrial pacing[11] or the cold pressor test.[9] These interventions may be associated with different changes in left ventricular filling depending on how the intervention influences cardiac output, contractility, and relaxation.

Several factors other than age and heart rate are known to influence filling in normal subjects. Variation with respiration[13] can be minimised by performing the recordings during quiet respiration and taking the mean of several measurements. The influence of blood pressure and left ventricular hypertrophy in normal subjects are at least partly explained by differences in age.[4 8] Differences in preload, which occur with changes in position may be important.[14 15] On the other hand studies have shown that Doppler indices of filling are not influenced by sex,[8 16] body surface area,[4 16] or an increase in left ventricular mass associated with athletic training.[17]

The relations between a diastolic index, age, and heart rate are almost certainly altered in patients with abnormal diastolic filling.[18 19] Keucherer *et al* showed that the relation between age and the A:E ratio measured by Doppler was different in patients with coronary artery disease.[18] Disease effects are of unknown size, vary between patients, and occur on top of age and heart rate effects. A practical approach is to measure the difference in filling from the measurement expected for the subject's age and heart rate.

Occult coronary artery disease may be present in some of the subjects studied. This disadvantage was accepted to obtain a large study population across a wide range of ages. Coronary artery disease in symptom free patients taking no treatment has not been shown to influence left ventricular filling.

The calculations can be done simply with a pocket calculator. The formulas used, however, to adjust for age and heart rate and the normal ranges for measurements depend on a standard technique. Filling measurements are influenced by sampling position,[20] and adjustment for measurements made at the mitral annulus would be different.

The calculation of a predicted normal value and a normal range for measurements of diastolic filling allows a more accurate assessment of the effects of disease on left ventricular filling in individual patients.

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Br Heart J 1992;68:613–5

TECHNIQUE

Percutaneous balloon pericardiotomy in the management of recurrent malignant pericardial effusions

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Abstract

Two patients with recurrent symptomatic pericardial effusions secondary to malignant disease were successfully treated by percutaneous balloon pericardiotomy. Open surgery was avoided and the procedure was completed under local anaesthesia in less than 40 minutes. The first patient was free of recurrence at nine months but pericardial effusion recurred at two months in the second patient.

Percutaneous balloon pericardiotomy offers a potentially important new means of relieving recurrent tamponade and substantially reduces trauma to the patient.

(*Br Heart J* 1992;68:613–5)

Recurrent symptomatic pericardial effusions can complicate malignant disease. They usually lead to increasing breathlessness as the tamponade develops. When conventional catheter drainage does not relieve symptoms and prevent recurrence the creation of a pericardial window by open surgical techniques has until now been the only other available treatment.[1] Unfortunately a 30 day mortality of up to 60% has been reported: this probably reflects the severity of the systemic illness.[2] A safe and effective non-surgical method to relieve symptoms in these patients would avoid the risks of general anaesthesia and surgery. Palacios *et al*[3] reported on the effectiveness of creating a pericardial window with a percutaneous balloon technique and in a multicentre study of 55 patients the success rate was 93%.[4]

We report our experience of this technique in the management of two patients with recurrent malignant pericardial effusions.

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Patients and methods

METHOD

The procedure was performed in the cardiac catheterisation laboratory with aseptic technique under fluoroscopic and echocardiographic guidance. The patients were sedated with intravenous diazepam, and intravenous pethidine was administered for analgesia. Local anaesthesia was achieved with 1% lignocaine.

We used a percutaneous subxiphoid approach to insert an 0·32 inch guide wire into the pericardial space. A 7 French pigtail catheter was passed over the wire. After 500 ml of fluid was removed to relieve symptoms the catheter was withdrawn and the wire was left in place. A 14 F dilator was inserted through the fibrous and parietal pericardium over the wire (fig 1). A low profile balloon dilating catheter (23 mm diameter, 4 cm long) (Mansfield Scientific) was exchanged over the wire and advanced into the pericardial space. The balloon was partly inflated with a mixture of contrast medium and saline under low pressure and gradually withdrawn until the waisting of the balloon by the pericardium was at its midpoint (fig 2). The balloon was then manually inflated to its maximum pressure of 3·5 atmospheres until the waisting disappeared (fig 3). It was kept inflated for five minutes.

A 7 F pigtail catheter was then exchanged over the wire and the effusion was completely drained. The pigtail catheter was left in place and drained every four hours for 24 hours. The catheter was removed after complete resolution of the effusion had been confirmed by echocardiography. A chest *x* ray was taken before, immediately after and 24 hours after the procedure to exclude a pneumothorax.

PATIENTS

Both patients had had two previous pericardiocenteses for relief of cardiac tamponade. In both cytology of the pericardial fluid showed a metastatic adenocarcinoma.

Case 1

The first patient was a 44 year old women with a four year history of ductal carcinoma of the breast. She had been managed with post-operative radiotherapy to the right chest wall and had had adjuvant hormonal therapy. In addition she subsequently received systemic chemotherapy for metastatic cutaneous disease and pulmonary metastases. Four months before percutaneous balloon pericardiotomy she had presented with cardiac tamponade which was relieved by pericardiocentesis. Cardiac tamponade recurred one month later and as the patient was keen to avoid open surgery, pericardiocentesis was repeated. She remained symptom free for three months until peri-

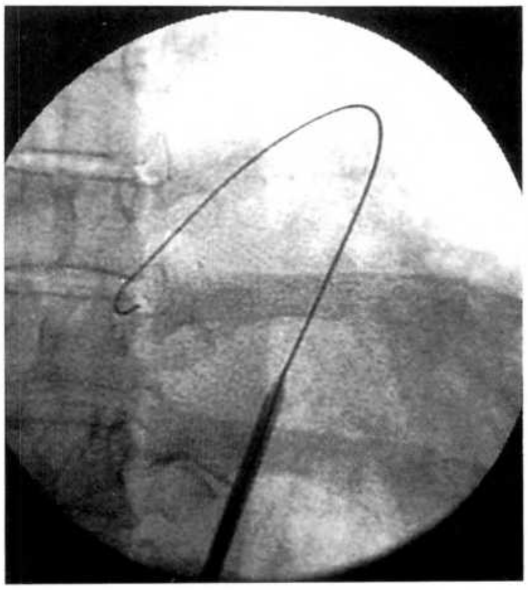

Figure 1 Guide wire in pericardial space and dilating sheath in situ.

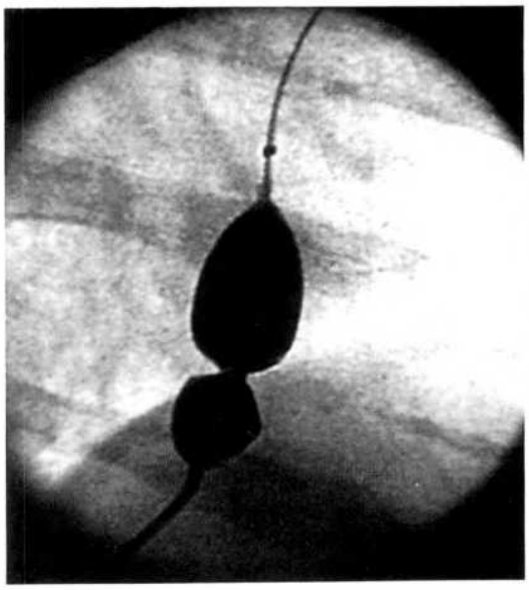

Figure 2 Fluoroscopy showing waisting of the balloon by the pericardium.

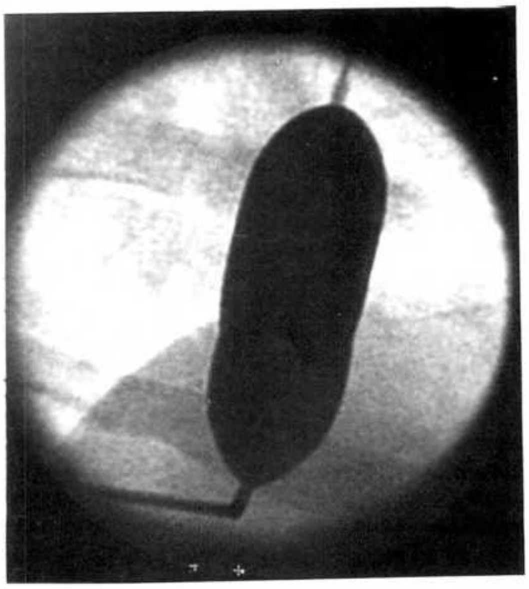

Figure 3 Fluoroscopy showing minimal residual waisting of the balloon after full inflation and creation of a window in the pericardium.

cardial effusion recurred and percutaneous balloon pericardiotomy was performed.

Case 2

The second patient was a 47 year old man who had presented nine months earlier with haemoptysis and pericardial tamponade which was managed with pericardiocentesis. Cervical and axillary lymph node histology showed a poorly differentiated adenocarcinoma: the site of the primary tumour, however, remains undetermined. Despite systemic chemotherapy, the pericardial effusion recurred after six months and a second pericardiocentesis was performed. Nine months later when the effusion again recurred percutaneous balloon pericardiotomy was performed.

Both patients tolerated the procedure very well but the first patient found the moment of balloon dilatation painful. So the second patient was given more analgesic and he felt no pain throughout the procedure. They were both ambulant 24 hours after the procedure. Their prognosis was poor, and they were pleased to have avoided open surgery.

Both patients were followed up with serial echocardiography. The first patient was free of recurrence of pericardial effusion (< 1 cm) at nine months but a pericardial effusion recurred after two months in the second patient. He had a further pericardiocentesis, and three months later he died of a pulmonary embolus.

Discussion

Recurrent pericardial effusions leading to tamponade are an uncommon but distressing manifestation of malignant disease. When repeated aspiration has been unsuccessful management has included instillation of chemotherapeutic agents, radiotherapy, indwelling catheter drainage, or open surgery to the pericardium under general anaesthesia. There is no convincing evidence that instillation of therapeutic agents into the pericardium improves the clinical outcome and it can be associated with patient discomfort; radiotherapy carries a risk of cardiac damage; and prolonged indwelling pericardial catheter drainage carries a risk of introducing infection.

Because many patients are systemically ill surgery that can adversely affect the general condition of the patient is best avoided.

Ziskind *et al*[4] reported the experience of the American registry of percutaneous ballon pericardiotomy and cited a 93% success rate (51 of 55 patients). In 48 patients malignancy was the cause of tamponade. Thirty two of these patients had died at 3·3 months with no recurrence of tamponade. Pleural effusions needing drainage occurred in eight patients and the four patients in whom drainage was unsuccessful had surgical procedures.

We report the use of percutaneous balloon pericardiotomy in the treatment of two patients with recurrent malignant effusions. The recurrence of pericardial effusion in our second patient is of interest. It has previously been shown that whereas survival after open surgery is not influenced by the extent of pericardial resection, recurrence of pericardial effusion is more common in patients who have a limited pericardiotomy (2 × 2 cm) rather than a more extensive pericardial resection.[2] It seems that percutaneous balloon pericardiotomy which produces a tear in the pericardium of approximately 2·0 cm in diameter,[5] is likely to be most useful in patients with terminal disease who may not live long enough for a recurrence to develop. Additionally, balloon pericardiotomy may be performed at more than one pericardial site through one percutaneous puncture. This may possibly offer further protection from recurrence of pericardial effusion after percutaneous balloon pericardiotomy.

Percutaneous balloon pericardiotomy seems to be useful in patients with malignant disease and a short life expectancy. It avoids the morbidity and the discomfort of open surgery in terminally illpatients. It has the advantages of avoiding general anaesthesia, of being a relatively short procedure, and of facilitating rapid mobilisation. A carefully controlled study is required to determine whether its use can be extended to tamponade with other aetiologies and whether it is effective for longer periods.

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Addendum

A United Kingdom registry for percutaneous balloon pericardiotomy is being formed. Please contact GJ for further information.

Br Heart J 1992;68:616–8

CASE REPORTS

Pulmonary artery rupture in pregnancy complicating patent ductus arteriosus

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Abstract
Fatal haemopericardium in a 27 year old pregnant woman was caused by rupture of a dissecting aneurysm of the pulmonary artery. She had an uncorrected patent ductus arteriosus and severe pulmonary hypertension. The wall of the pulmonary artery showed atherosclerosis and cystic medionecrosis.

(*Br Heart J* 1992;**68**:616–8)

Case report
A 27 year old West Indian woman with a patent ductus arteriosus had been clinically well and took no medication. Cardiac catheter studies when she was 13 years old had shown pulmonary hypertension with pressures of 70/40 mm Hg. There was reversal of the shunt during exercise (right-to-left), indicating that she was unsuitable for surgery and therefore the patent ductus had remained uncorrected. On examination, the apex beat was displaced laterally to the anterior axillary line and there were signs of pulmonary hypertension—loud pulmonary heart sound (P_2) and a palpable pulmonary artery. There was a long early diastolic murmur of pulmonary regurgitation and an ejection systolic murmur. An electrocardiogram showed evidence of right ventricular hypertrophy.

Her first pregnancy, when she was 25 years old, had been uneventful; however, there had been clinical signs of increasing pulmonary hypertension. At 38 weeks' gestation a normal female infant was delivered through the vagina. Immediately post partum the mother developed a pyrexia, which was thought to be endocarditis, and this settled on antibiotics. She was strongly advised to avoid further pregnancy.

The second pregnancy, two years later, was progressing well and she was admitted to hospital for bed rest. She died unexpectedly in bed at 33 weeks' gestation.

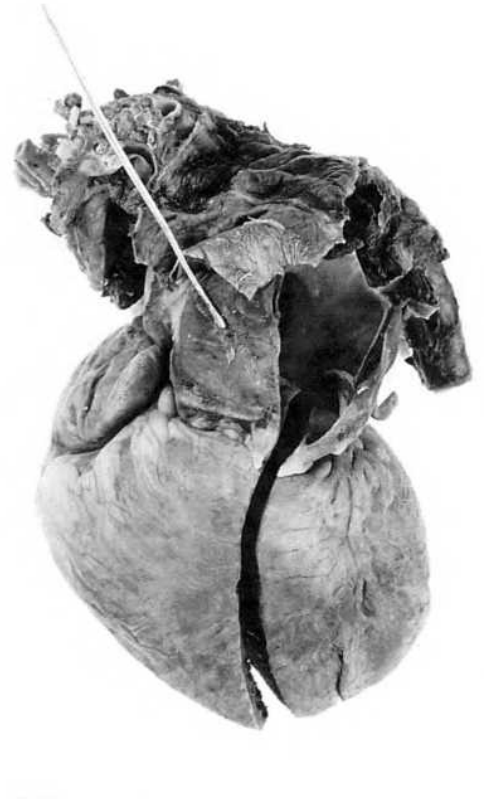


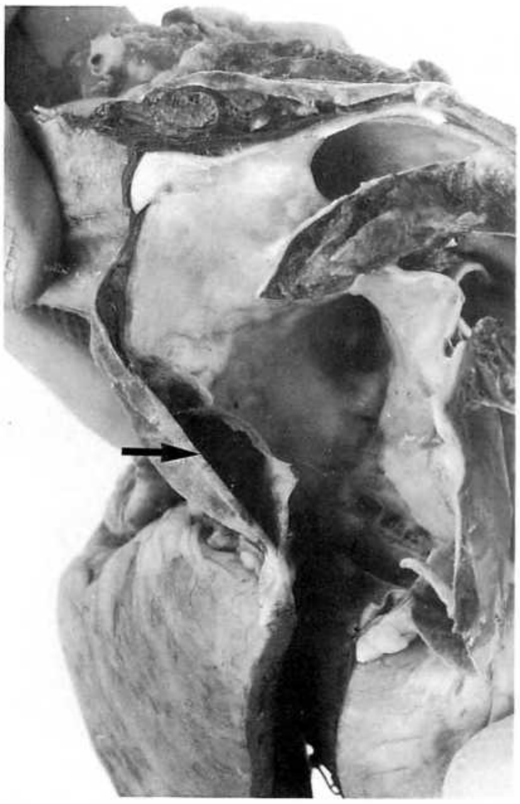
Figure 1 Necropsy appearance of the heart and pulmonary artery, showing dilatation of the main pulmonary artery and right ventricular hypertrophy. The probe marks the site of pulmonary artery rupture.

Necropsy and histological findings
The body was thin but well nourished (height 163 cm, weight 54·6 kg). There was a large haemopericardium caused by rupture of a dissecting aneurysm of the main pulmonary artery into the pericardial sac at the base of the heart. The main pulmonary trunk was dilated to 5 cm in diameter and the dissection originated in a raised atheromatous plaque on the anterior aspect of the pulmonary artery 3 cm above the pulmonary valve (figs 1 and 2). There was a large patent ductus arteriosus (diameter 2 cm) leading to an aorta of normal calibre. The right ventricle was hypertrophied (100 g). The left ventricle including the septum weighed 160 g. There was no other gross cardiac malformation.

Histological examination of the main pulmonary artery showed a striking accumulation of alcianophilic mucopolysaccharide in the media (cystic medionecrosis) (fig 3) with dissection between the inner and outer halves. There were also small amounts of medial alcianophilic mucin in the aorta. In the lungs there were widespread severe hypertensive changes with plexiform lesions (plexigenic pulmonary arteriopathy).

No other anatomical or histological abnormality of significance was seen and the fetus was normal.

Figure 2 Necropsy appearance of the opened main pulmonary artery, showing atherosclerosis. The arterial dissection is seen in the cut edge of the pulmonary trunk (arrow).



Discussion

Pulmonary artery aneurysm is a rare condition and is invariably associated with pulmonary hypertension. In a necropsy review of 111 cases,[1] pulmonary hypertension due to cardiac malformation was present in 66%. Patent ductus arteriosus was the commonest single lesion, occurring in combination with 22% of aneurysms.

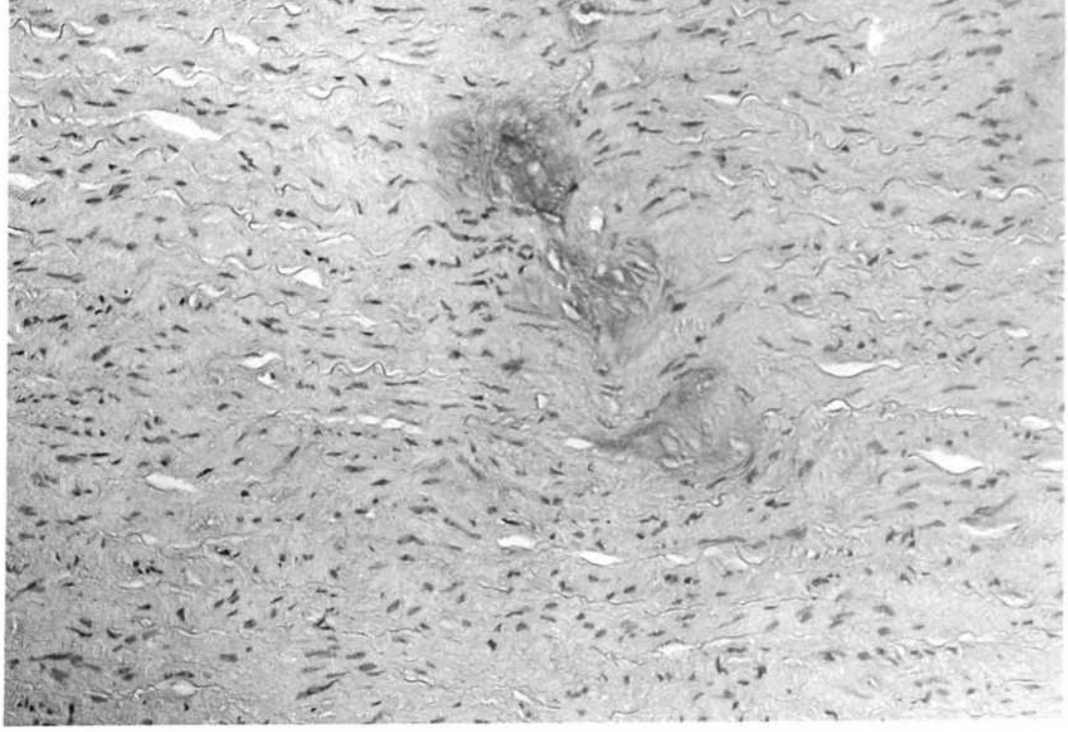
When Coleman *et al*[2] reviewed published reports they found only six cases of ruptured pulmonary artery aneurysm associated with patent, ductus arteriosus alone, in addition to their own. There have been reports of two more cases.[3 4] We identified only one report of rupture in pregnancy,[5] however, this was associated with pulmonary infundibular stenosis as well as patent ductus arteriosus. There is also a report of a maternal death occurring 17 hours post partum owing to pulmonary artery dissection associated with a patent ductus alone,[6] presumably precipitated by labour. Our case is the only report we found of rupture during pregnancy associated with a patent ductus as the only anatomical abnormality.

Cystic medionecrosis is usually associated with dissection of the pulmonary artery[3] as is atheroma and our case is no exception. Indeed both are known to be related to severe pulmonary hypertension.

This case emphasises the possibility of arterial dissection in pregnancy, particularly in the presence of pre-existing cardiovascular disease. This association has been well described previously, in particular by Guthrie and MacLean[7] who showed that nine of 57 non-aortic arterial dissections in women occurred either during pregnancy or shortly after delivery.

It is of interest to speculate on the cause of the apparently increased incidence of both systemic and pulmonary arterial dissections in pregnancy. It has been suggested that the increase in body water in pregnancy is in part taken up by connective tissue mucopolysaccharides.[8] Robertson pointed out there is no reason why mucopolysaccharides in the vessel

Figure 3 Histological section showing pools of mucopolysaccharide in the media of the pulmonary artery (haematoxylin and eosin; original magnification, × 500).



wall should not be involved in this process[9]; indeed there is some histopathological evidence that they are.[10] We suggest that the likeliest course of events in our case was cystic medionecrosis and atheroma, followed by dissection and rupture. These were consequent upon the increased cardiac output and exaggeration of mucopolysaccharide deposition associated with pregnancy.

We thank Dr R M Whittington, HM Coroner for the District of Birmingham and Solihull for permission to report this case.

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Br Heart J 1992;**68**:619–20

Leaking false aneurysm of right coronary saphenous vein graft: successful treatment by percutaneous coil embolisation

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Abstract

An unusual complication after aortocoronary bypass grafting (CABG) is described in which a false aneurysm of the saphenous vein graft to the right coronary artery (RCA) developed and caused profuse intermittent bleeding through the sternotomy wound. The aetiology of this condition is uncertain but it could occur whenever a suture line is present especially in the presence of infection. The diagnosis was made non-invasively by a contrast enhanced computed tomogram and was subsequently confirmed by selective coronary bypass angiography. The pseudoaneurysm was successfully obliterated by coil embolisation of the right coronary graft, which stopped the bleeding immediately and was followed by rapid wound healing.

(*Br Heart J* 1992;**68**:619–20)

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Profuse haemorrhage caused by secondary infection of an anastomotic suture line is a well recognised early complication after coronary artery surgery. Less commonly, false aneurysms of the ascending aorta may develop at the site of an aortic incision and present clinically or may be detected at necropsy, though they have seldom been reported in published reports.[1 2] False aneurysms related to coronary vein grafts are, however, unusual and difficult to treat.[3] Because the presentation of these conditions is generally dramatic and the mortality associated with acute rupture is high, immediate surgical intervention has hitherto been the only available treatment, despite being attended with a high morbidity and frequently an unpredictable outcome.

We report a case in which a false aneurysm of the saphenous vein graft to the right coronary artery developed and caused frequent episodes of profuse intermittent bleeding through the sternum with failure of sternal wound healing. As an alternative to surgical management we used emergency coil embolisation of the vein graft, a technique that we believe has not been used before in such a case.

Case report

A 63 year old man with a long history of angina was investigated in 1989 and found to have extensive triple coronary artery disease with reduction of left ventricular function caused by hypokinesia of the inferior segment. At that time he was also known to have diffuse peripheral vascular disease of both ileofemoral segments and a right profundaplasty had been performed a year before. Coronary artery bypass surgery was undertaken in September 1990 and an internal mammary artery was applied to the left anterior descending coronary artery and vein grafts to the distal right and obtuse marginal vessels. The patient's subsequent progress was complicated initially by major secondary haemorrhage from an infected tear in the ascending aorta after staphylococcal wound infection and sternal dehiscence: the tear was thought to have been a direct consequence of repeated sternal friction and erosion of the right lateral wall which lay close to the vein graft anastomoses. Through a considerably restricted access, the friable area was successfully repaired with a vein patch. The sutures were applied under direct vision. Recurrent sternal wound infections over several weeks, which required close observation, delayed his discharge from hospital. The sternotomy wound seemed to heal slowly and he required readmission after repeated minor episodes of haemorrhage from an area of infected granulation tissue in the middle of the sternotomy incision. Further episodes of minor bleeding often occurred and on one occasion he had a massive life-threatening haemorrhage.

A dynamic computed tomogram showed a pool of extravascular contrast medium behind and erosion through the inner table of the sternum. A track could be identified that almost certainly originated from the proximal segment of a vein graft. A flase aneurysm from the ascending aorta could not be excluded because of the initial aortic bleed after surgery. Aortography and selective vein graft angiography (fig 1) confirmed the presence of a false aneurysm originating from the proximal third of the graft to the right coronary artery. The distal part of that vessel was still patent though the run off was sluggish. This factor coupled with the presence of hypokinesia of the inferior segment led us to think that occluding this vessel would not cause a significant area of infarction. The possibility of surgical correction was also considered but was thought to carry too high a risk. Embolism of the right coronary artery graft was therefore regarded as the only realistic alternative.

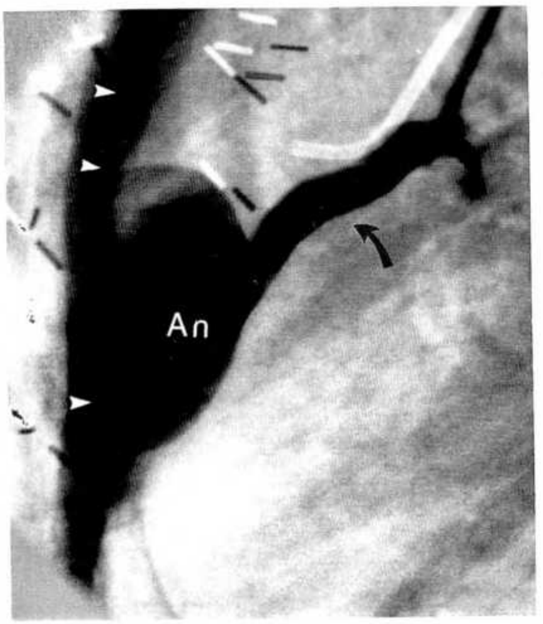

Figure 1 Selective coronary angiogram of a right coronary vein graft (curved arrow). A large false aneurysm (An) arising from the proximal third of the vein graft can be seen adherent to the sternum with extravasation of contrast medium into the retrosternal region (arrow heads).

The graft was gauged to be a vessel with a 6 mm diameter, but at the time of emergency intervention only 5 mm and 8 mm coil emboli were available. An 8 mm coil was placed in the mid portion of the graft but owing to the disparity in size and the turbulent bi-directional flow between the graft and the aneurysm, the coil was dislodged into the systemic circulation and wedged in the left common iliac artery. Fortunately, this proved to be clinically inconsequential. A 5 mm coil was too small and was carried by the forward flow into the false aneurysm sac. The catheter was advanced to the mouth of the aneurysm and a further 8 mm coil was placed, straddling the vein graft and the ostium of the false aneurysm to provide a framework for the insertion of further 5 mm and 3 mm coils. These reduced flow and subsequently occluded the graft (fig 2). Heated contrast medium (iopamidol 370 at 80°C) was also instilled to promote thrombus formation.[4]

The patient tolerated this procedure remarkedly well. The bleeding stopped immediately and the sternal wound healed rapidly over the next two weeks (fig 1B). Serial electrocardiograms and enzyme estimations showed no evidence of myocardial damage after occlusion of the right coronary graft. Transient renal dysfunction caused by the contrast medium resolved rapidly within a few days on conservative treatment. The patient continues to do well with adequate peripheral circulation and his claudication distance unchanged.

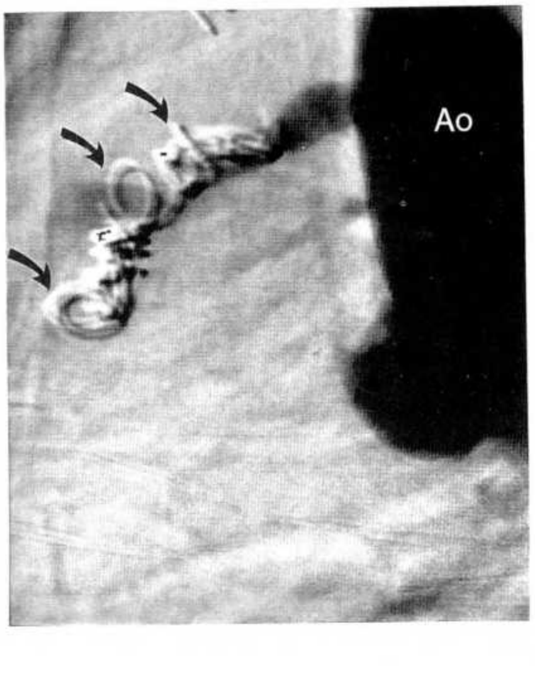

Figure 2 Post-embolisation aortic root (Ao) angiogram. A series of coils (arrowed) have occluded the vein graft, completely obliterating the false aneurysm.

Discussion

The occurrence of false aneurysms after aortocoronary surgery is a rare but potentially lethal complication attended with high morbidity that is difficult to treat. Traditionally, the management has been surgical but because successful intervention has seldom been reported, optimal treatment has usually been determined by the personal experience of the clinician. In view of the site of the aneurysm in our patient we believed that it could not be safely managed by further sternotomy: alternative surgical approaches were regarded as equally hazardous. Embolisation of the vein graft feeding the false aneurysm was considered the most appropriate treatment.

Several individual case reports have described false aneurysms arising from the aorta, commonly in relation to a suture line and often as a consequence of secondary infection after operation. In our case, it was clinically unclear whether the aneurysm originated in the aorta or from the vein graft itself. A computed tomogram, however, suggested a vein graft origin and this was conclusively demonstrated by selective angiography.

The only technical difficulties associated with the procedure were related to the lack of suitable coil sizes. It had been estimated angiographically that the vein graft was a 6 mm diameter vessel but only 5 mm and 8 mm coils were available. Nonetheless, profuse bleeding meant that intervention was urgent. Correct sizing and scrupulous placement of these devices are fundamental to the successful obliteration of the vessel. The initial coil must be sufficiently large to wedge against the wall of the conduit and provide a matrix for subsequent coils. The thrombogenic nature of these occluders together with the resultant sluggish flow hold the coils tightly into position until a secure thrombus firmly obliterates the vessel permanently.

Intervention was judged to be successful when a computed tomogram showed occlusion of the vein graft and obliteration of the false aneurysmal sac, bleeding did not recur, and the wound healed rapidly. This technique was clearly better than a surgical approach and we regard embolisation as the best treatment for false aneurysms of vein grafts after coronary artery surgery.

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Br Heart J 1992;68:621–9

BRITISH CARDIAC SOCIETY

Seventh survey of staffing in cardiology in the United Kingdom 1991

From the British Cardiac Society, the Cardiology Committee of the Royal College of Physicians, and the Trafford Centre for Medical Research, University of Sussex

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Abstract
The Seventh Survey of Staffing in Cardiology was conducted with an index date of 31 July 1991. At that time the total number of posts for cardiologists in England and Wales, defined as individuals trained in the specialty and spending at least 40% of their professional time working in it, was 340. Ten individuals worked part time only, making 335 whole time equivalent posts. This number increased from 1990 by 15 (4·7%). There were 67 cardiologists in Scotland and Northern Ireland, making a total for the United Kingdom of 407 posts (402 whole time equivalents). Sixteen Districts in England and Wales had no cardiologist at the time of the survey, and 31 other Districts had less than seven visiting sessions each week. The situation had not improved since the 1990 survey. The population of these 47 Districts is nearly nine million. Scotland had almost 800 000 additional people served by Health Boards without resident cardiologists.

The number of senior registrars and lecturers is inadequate to provide a full period of training for most who advance to consultant status, and the situation will worsen from 1995 onwards. A major problem has been a top slice of 10 posts for a research allocation, few of which are occupied by individuals seeking a career in the specialty. These posts should be redesignated to increase training opportunities to counter the present shortfall and facilitate an expansion in consultant posts of at least 5% per annum over the next decade.

(*Br Heart J* 1992;68:621–9)

The first staffing survey for consultant and senior registrar posts in cardiology related to 1979 and 1980 and was published in 1981.[1] Thereafter the staffing surveys were biennial[2-5] until 1990 when a decision was made to monitor changes each year. The present survey, with an index date of July 1991, is therefore the first of a new series that will be annual. The increase in the frequency of surveys was deemed necessary because of the rapid changes occurring within the National Health Service and because of our concerns that senior registrar numbers were not being adjusted sufficiently rapidly to avoid a dearth of fully trained individuals to fill consultant vacancies.

The surveys have become more complex—and in general more accurate—over the past decade. In this survey, therefore, we have more detailed information than was available previously. A few previous errors have come to light (mostly relating to the 1986 survey that was completed by the Trafford Centre, but started elsewhere). We have also made some minor amendments to definitions to reflect changes in medical practice. For these reasons the 1991 data may not be strictly comparable to those published in previous surveys. But the comparisons we have made in this paper have been adjusted for these minor discrepancies except when otherwise specified.

Methodology

Although the index date for the current survey was July 1991, the survey did not begin until October of that year. The first stage was to identify individuals who should be counted as cardiologists or physicians with a major interest in the specialty. Previously we have relied on information from one contact in each Regional Health Authority, but this method may become less accurate with the increasing autonomy of district hospitals whether they have Trust status or function as directly managed units. We therefore approached instead one contact in each Health District of England and Wales and one contact in each Area Board of Scotland and Northern Ireland. We listed for them the names that we had already on file for individuals within their own Districts or Boards, with the request that they should draw our attention to any who had retired or died, and add names of any who could conceivably fall within our definitions. In January 1992 we sent 443 detailed questionnaires to all consultants who had been identified in the first stage of the survey. The net was deliberately cast wide and included some district physicians who had not previously been included on our database. In general we had excellent cooperation, and within six weeks 82% of the forms had been returned. Unfortunately we had considerable difficulty with many of the remainder.

Reminder letters and duplicate forms were sent on three occasions, and all data were available only in early August. As the replies came back the information was compared with that already available on file, and some inconsistencies had to be resolved. Some questions were not completed on the first questionnaire and some responses were inappropriate—no doubt reflecting deficiencies in the forms. For example, some physicians in smaller district hospitals claimed incorrectly to practise interventional cardiology because we had not defined the meaning of that term.

After all the information had been completed, processed, and checked for omissions and errors it went through one final stage of verification. Tables giving all relevant data (except for planned retirement dates, which we regard as confidential) were sent to Regional contacts for scrutiny, and where necessary further minor changes were made. This three stage process is time consuming, but for the first time most information had been provided by individuals rather than by selected nominees in Regions and Districts. The detailed checking and cross checking has ensured that the data are as accurate as we can make them.

We continue to have difficulty in one important area, but the problem is inevitable. This relates to the type of work undertaken by cardiologists. The individuals in our survey are divided into four categories: first into those who practise either adult cardiology on the one hand or practise paediatric cardiology on the other, and secondly those who are regarded as spending all their professional time in the specialty (designated "cardiology only") and those who also have a commitment to general internal medicine (designated as having a "major interest" in the specialty). We have no difficulty in establishing whether practice is adult or paediatric, but the sessional commitment to the specialty is harder to define and inconsistencies have occurred from year to year—often because the information that we have been given has varied. Alteration of one of our definitions has compounded the problem. Many fully trained cardiologists working in cardiac centres and practising invasive and interventional cardiology do retain some commitment to general medical "take", and indeed this may well become more common as emphasis on specialised medicine increases and fewer physicians are regarded as generalists. We had been inconsistent in previous surveys, in that a commitment to "take" for emergency admissions sometimes influenced the category but sometimes did not. We now define a whole time commitment to the specialty (that is, "cardiology only") as "spending 80% or more of professional time in cardiology" so that having a general medical "take" is no longer—by itself—a decisive factor in deciding the appropriate category for a cardiovascular physician. This new definition has meant that a few individuals previously listed as having a "major interest" are now designated as practising "cardiology only". The total numbers, of course, are not affected. The definition of a physician with a "major interest" in cardiology requires that an individual must have had appropriate training in the specialty and must spend at least 40% of his or her professional time working exclusively within it. The major difficulty here relates to the training, which is clear cut for those appointed in recent years but more difficult for those who were senior registrars when training programmes were less clearly defined. This difficulty becomes less important as the years pass, but still gives rise to the occasional inconsistency.

Most consultants spend less than the 11 notional half days in hospital practice. For the purposes of the survey, however, they are counted as one whole time equivalent if they have seven sessions or more. Those with six sessions or less are counted as holding a part time post which—for simplicity—counts as 0·5 of a whole time equivalent. We must stress, however, that academic sessions and service sessions are regarded equally (a point sometimes misunderstood by those who complete our questionnaires).

One of the important functions of our survey is to identify districts that do not have adequate cardiological cover. We still have many district general hospitals without any individual who can be defined as a cardiologist according to the criteria mentioned above—a position that we regard as wholly unsatisfactory. In some cases provision is made by a visiting cardiologist, often from the Regional centre. We regard seven sessions as the minimum that will qualify a District as having cardiological cover. In this survey—but not in previous ones—we have distinguished those Districts that have no cover provided by a cardiologist listed in our survey from those that have inadequate (that is, less than seven sessions) cover.

A major centre has been defined as a cardiac

Table 1 Cardiovascular physicians in England and Wales, 1980–1991

	*Cardiology only**		*Major interest*		
Year	*Adult*	*Paediatric*	*Adult*	*Paediatric*	*Totals*
1980	103	19	98	3	223
1982	111 (8)	18 (−1)	117 (19)	4 (1)	250 (12·11%)
1984	111 (0)	29 (11)	121 (4)	6 (2)	267 (6·80%)
1986	119 (8)	31 (2)	118 (−3)	2 (−4)	270 (1·12%)
1988	130 (11)	33 (2)	128 (10)	0 (−2)	291 (7·78%)
1990	145·0 (15·0)	39·0 (6·0)	134·0 (6·0)	2·0 (2 0)	320·0 (9·97%)
1991	166·5*(21·5)	42·0 (3·0)	124·5* (−9·5)	2·0 (0·0)	335·0 (4·69%)

The numbers in parentheses show change in numbers over the previous survey. The final column shows total percentage changes over the previous survey. Starting from 1990, figures are shown in whole time equivalents.

*"Cardiology only" physicians were re-defined in 1991 from "spending virtually the whole of their time in cardiology" to "spending more than 80% of their time in the specialty", giving a disproportionate change in numbers over 1990.

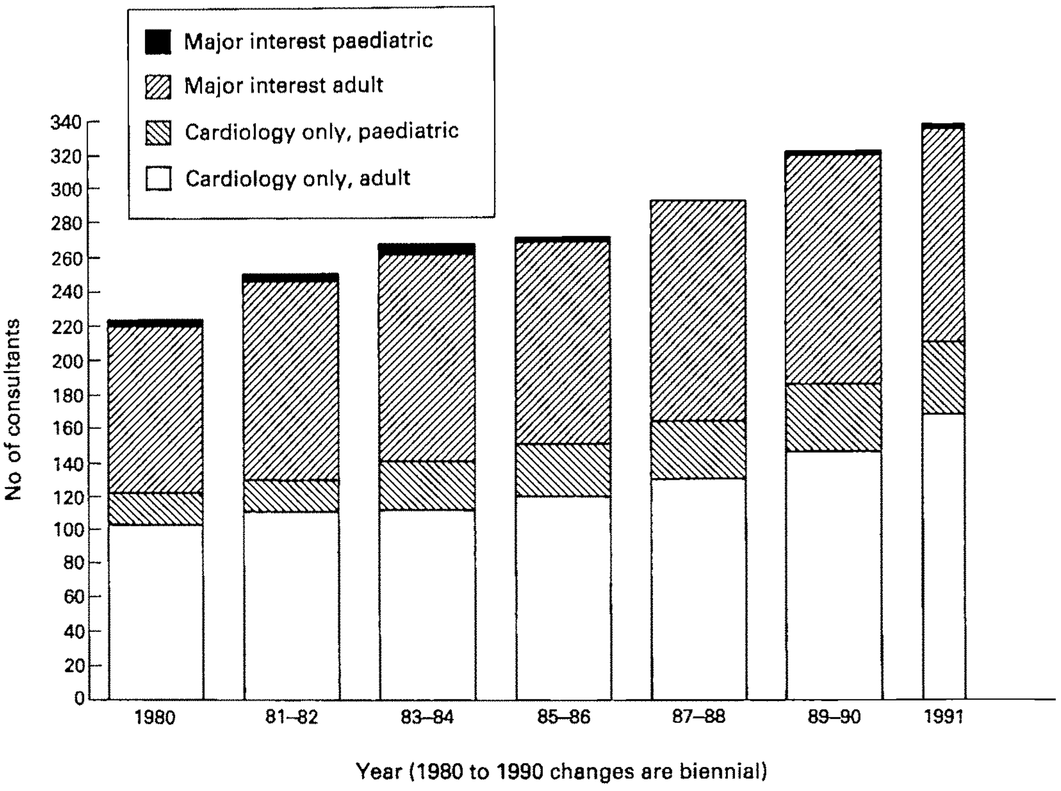


Figure 1 Cardiovascular physicians England and Wales, 1980–1991.

unit that has full investigatory facilities plus cardiac surgery.

The data

Relevant information from the 1991 survey is presented, as usual, in tables and graphs with a similar format to that used previously. Some general points should be noted. Blanks represent either zero values or data that are considered inappropriate. They do not imply missing values. Population figures have been obtained from the Office of Population Censuses and Surveys. They are estimates for mid 1990 (not 1991) and are given in thousands (with the figure after the decimal point representing hundreds rounded up or down). The hospitals that fall within the orbit of the Special Health Authority are considered separately, though they fall within the boundaries of North East and North West Thames Regional Health Authorities. It should be noted that Wales has nine Health Districts but 18 district general hospitals, whereas in England the usual pattern is for one district general hospital within one Health District. The arrangements for Scotland and Northern Ireland are different. There are no District Health Authorities, but instead Area Boards which may have responsibility for more than one district general hospital. Where appropriate, 1990 data are given in parentheses. The following abbreviations are used in the tables: HD, Health District; HB, Health Board; HSSB, Health and Social Services Board; MC, major centre; WTE, whole time equivalent; SR, senior registrar.

Table 2 Cardiovascular physicians by Region of England and Wales (31 July 1991)

Region	*Population mid 1990*	*HDs*	*MCs*	*Cardiology only (WTEs)*		*Major interest (WTEs)*		*Total WTEs*	*Total individuals*
				Adult	*Paediatric*	*Adult*	*Paediatric*		
East Anglia	2059·0	8	1	6·5 (4·0)		3·0 (5·5)		9·5 (9·5)	10 (10)
Mersey	2402·8	10	2	6·0 (4·0)	3·0 (3·0)	6·0 (6·0)		15·0 (13·0)	15 (13)
NE Thames	3802·9	16	3	16·0 (15·5)		9·0 (9·0)		25·0 (24·5)	24 (25)
NW Thames	3498·6	13	2	15·0 (11·0)	2·0 (1·0)	6·0 (7·0)	1 (0)	24·0 (19·0)	24 (19)
North Western	4016·1	19	3	10·0 (9·0)	3·0 (3·0)	11·0 (12·0)		24·0 (24·0)	24 (24)
Northern	3075·4	16	1	8·5 (8·5)	3·0 (3·0)	9·0 (9·0)		20·5 (20·5)	21 (21)
Oxford	2563·9	8	1	4·0 (4·0)	2·0 (2·0)	8·0 (7·0)		14·0 (13·0)	14 (13)
SE Thames	3658·2	15	4	16·0 (15·0)	4·0 (4·0)	9·0 (9·0)		29·0 (28·0)	30 (29)
SW Thames	2978·6	13	1	12·0 (9·0)		4·0 (6·0)	0 (1)	16·0 (16·0)	16 (16)
South Western	3262·1	11	1	9·5 (6·0)	3·0 (3·0)	4·0 (5·0)		16·5 (14·0)	17 (14)
Trent	4704·5	12	2	10·0 (8·0)	2·0 (1·0)	11·5 (12·5)	1 (1)	24·5 (22·5)	25 (23)
Wessex	2940·3	10	1	3·0 (3·0)	3·0 (3·0)	10·0 (11·0)		16·0 (17·0)	16 (17)
West Midlands	5219·3	22	3	14·5 (14·0)	3·0 (3·0)	15·0 (15·0)		32·5 (32·0)	33 (32)
Yorkshire	3655·7	17	3	12·5 (12·0)	3·0 (3·0)	10·0 (11·0)		25·5 (26·0)	26 (26)
Wales	2881·4	9	1	5·0 (4·0)	1·0	9·0 (9·0)		15·0 (13·0)	15 (13)
Special hospitals		4	4	18·0 (18·0)	10·0 (10·0)			28·0 (28·0)	30 (28)
Totals	50 718·8	203	33	166·5* (145·0)	42·0 (39·0)	124·5* (134·0)	2 (2)	335·0 (320·0)	340 (323)

Additional number of staff-grade cardiologists: one "cardiology only", one "major interest".
*"Cardiology only" physicians have been re-defined in 1991 as "spending more than 80% of their time in cardiology". By our previous definition there were 7·5 more "cardiology only" adult and 4·5 more "major interest" adult posts than in 1990.
The figures above include six vacancies (two in paediatric cardiology).

Table 3 Cardiovascular physicians by Health Board in Scotland (31 July 1991)

Health Board	Population mid 1990	MCs	Cardiology only Adult	Cardiology only Paediatric	Major interest Adult	Major interest Paediatric	Totals
Argyll and Clyde	440·4				2 (2)		2 (2)
Ayrshire and Arran	375·4				2 (2)		2 (2)
Borders	103·5						
Dumfries and Galloway	148·4				1 (1)		1 (1)
Fife	345·9						
Forth Valley	272·1						
Grampian	506·1	1	3 (3)				3 (3)
Greater Glasgow	927·7	2	8 (9)	2 (3)	7 (6)	1 (0)	18 (18)
Highland	204·3				1 (1)		1 (1)
Lanarkshire	562·5				3 (3)		3 (3)
Lothian	749·6	1	7 (7)	2 (2)	1 (1)		10 (10)
Orkney	19·6						
Shetlands	22·3						
Tayside	394·0		2 (2)				2 (2)
Western Isles	30·7						
Totals	5102·4	4	20 (21)	4 (5)	17 (16)	1 (0)	42 (42)

Table 4 Cardiovascular physicians by Health Board in Northern Ireland (31 July 1991)

Health Board	Population mid 1990	MCs	Cardiology only Adult	Cardiology only Paediatric	Major interest Adult	Major interest Paediatric	Totals
Eastern HSSB	647·6	1	11 (11)	2 (2)	1 (2)		14 (15)
Northern HSSB	386·4		1 (0)		3 (4)		4 (4)
Southern HSSB	292·1				3 (3)		3 (3)
Western HSSB	262·5		2 (0)		2 (3)		4 (3)
Totals	1589·4	1	14 (11)	2 (2)	9 (12)	0 (0)	25 (25)

Comments

STAFFING: CONSULTANT GRADE

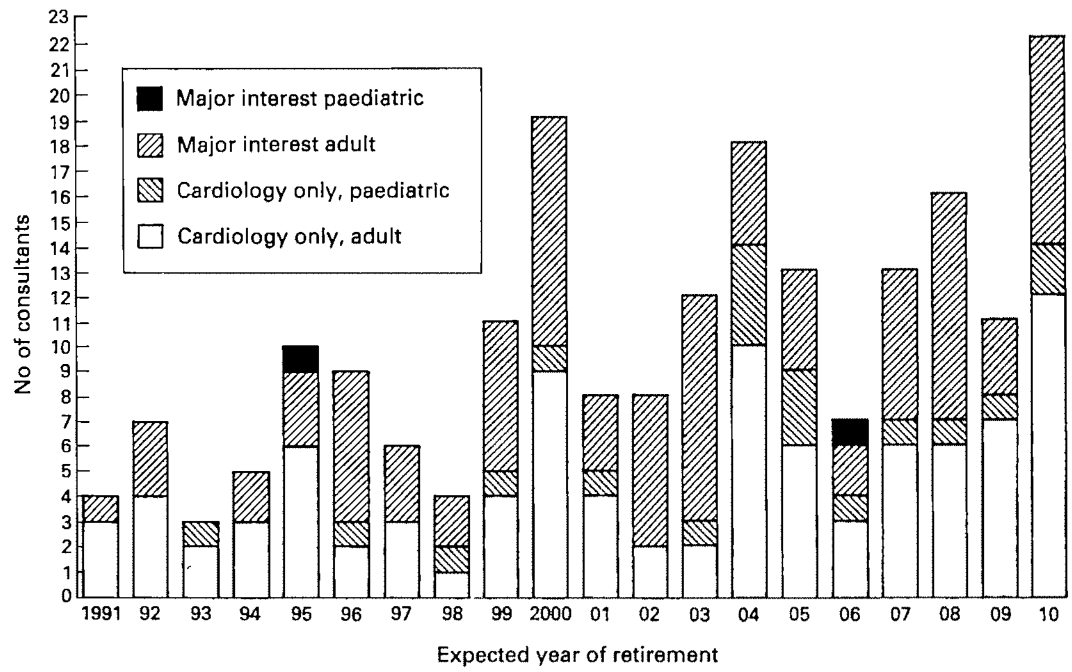
Table 1 shows that the number of cardiologists in England and Wales has increased progressively from 1980 to 1991 with only a very small apparent increase in 1986. This small increase was spurious. The 1986 survey was originally undertaken from the offices of the British Cardiac Society but was not completed at the time. The data—as they were available—were eventually published with the 1988 survey. Some of the errors from 1986 have been corrected only recently. The total increase from 1980 to 1991 is, however, substantially accurate. It shows an overall increase of 112 (50%), but the biennial growth has averaged only 7·6% (3·8% annual growth). Even the increase from 1990 to 1991 of 4·7% is marginally below the 5% "target" that we regard as reasonable. Most of the increase is seen in the column for adult "cardiology only" with an apparent decrease in numbers for adult "major interest". There was no real decline in the "major interest" posts: the change is due to the alteration in designation mentioned above. The alteration in designation does not, of course, affect the overall numbers but does reflect more accurately the varying commitments of cardiologists. After allowing for this change in designation there were 7·5 more "cardiology only" posts and 4·5 more "major interest" adult posts than in 1990. In the column for paediatric posts with a "major interest" the negative numbers reflect either changes in posts that became "cardiology only" or other changes in designation—there were no true losses. Figure 1 shows the increase in numbers of cardiologists that has occurred over an 11 year period. The last column is narrower because it shows data for only one year rather than two. There is slight distortion in the comparison between "cardiology only" and "major interest" in adult posts for the reason mentioned above.

Table 5 Number of retirements expected each year for cardiovascular physicians in England and Wales (as of 31 July 1991)

Year	Cardiology only Adult	Cardiology only Paediatric	Major interest Adult	Major interest Paediatric	Total
Vacancies	3	2	1		6
1991	3		1		4 (4)
1992	4		3		7 (2)
1993	2	1			3 (5)
1994	3		2		5 (4)
1995	6		3	1	10 (6)
1996	2	1	6		9 (5)
1997	3		3		6 (13)
1998	1	1	2		4 (5)
1999	4	1	6		11 (11)
2000	9	1	9		19 (14)
2001	4	1	3		8 (7)
2002	2		6		8 (12)
2003	2	1	9		12 (6)
2004	10	4	4		18 (12)
2005	6	3	4		13 (11)
2006	3	1	2	1	7
2007	6	1	6		13
2008	6	1	9		16
2009	7	1	3		11
2010	12	2	8		22
After 2010	73	20	35		128
Totals	171	42	125	2	340

Table 2 shows the total of cardiologists in each Region. In this survey we present an additional column so we show both total individuals and whole time equivalents. Ten cardiologists are working part time (that is, less than seven sessions of hospital practice). Two cardiologists share their time between two Regions, and in this table are therefore shown as a half post in each. Most Regions show an increase in numbers, though five are unchanged and two show a small decrease. The loss of one individual in Wessex represents a cardiovascular epidemiologist who moved to London

Figure 2 Retirements expected 1991–2010 England and Wales.



and was not replaced locally. The small change in Yorkshire was because of an alteration in sessional commitment for one individual. There has been no true loss within any Region. Marked discrepancies persist between the different Regions in the number of cardiologists per million population, ranging from 4·6 in East Anglia to 7·9 in South East Thames. The average for England and Wales was 6·6.

Tables 3 and 4 show comparable data for Scotland and Northern Ireland. There are no part time posts in these countries, so all figures represent individuals. In the Scottish data, two cardiologists have slightly reduced their commitment to the specialty so that they have changed from "cardiology only" to "major interest". One "major interest" post has become "cardiology only". The figures include one paediatric "cardiology only" post that was vacant on the date of the survey. There is no change overall in the number of consultants, but the ratio of cardiologists per million population at 8·2 is higher than in England and Wales. For Northern Ireland, the total number of cardiologists is unchanged overall at 25, with a ratio per million population of 15·7. There was one true gain in an adult "cardiology only" post. One of the apparent losses in the "major interest" post reflected an error in the previous survey. Other changes are due to alterations in designation.

Table 6 Number of retirements expected each year for cardiovascular physicians in Scotland (as of 31 July 1991)

	Cardiology only		*Major interest*		
Year	*Adult*	*Paediatric*	*Adult*	*Paediatric*	*Total*
Vacancies		1			1
1991					(1)
1992			1		1
1993					(1)
1994			1		1
1995			1		1 (3)
1997	1				1 (1)
1998	1		2		3
1999			1	1	2
2000			1		1 (2)
2002	1		1		2
2003	1	1			2 (2)
2004					(2)
2005	1		1		2 (3)
2006		1	2		3
2007	1		1		2
2008	3		1		4
2009	1				1
2010	2				2
After 2010	8	1	4		13
Totals	20	4	17	1	42

Years omitted: no retirements expected.

Table 5 and figure 2 show the number of retirements predicted from the date of the survey (31 July 1991) to the year 2010. The numbers in parentheses in table 5 show the corresponding predictions given with the 1990 data. One important change has occurred. The 1990 data showed an almost stepwise increase in the number of retirement vacancies predicted from 1997 onwards—a change that caused us considerable concern because of the predicted inadequacy in the number of trained senior registrars to fill these posts. Figure 2 shows a smoother increase than the corresponding figure in our previous publication. The change reflects the decision by many consultants to consider retirement earlier than they had previously planned. We have calculated the intended retirement age at the time of our last four surveys. On average, consultants in 1986 stated that they would retire at 64·22 years, in 1988 at 64·16 years, and in 1990 at 64 years. But by 1991 there had been a sharp decrease to 63 years. The number of retirements that occurred over the previous decade was fairly steady, averaging around six per annum with additional posts becoming vacant because of deaths and new appointments. The table shows that the pattern still changes fairly abruptly—not now from 1997 as previously predicted, but (because of earlier retirements) from 1995 onwards. Tables 6 and 7 show comparable data for Scotland and Northern Ireland. In these two countries there are far fewer posts. Though the tables show no clear evidence of any trend

Table 7 Number of retirements expected each year for cardiovascular physicians in Northern Ireland (as of 31 July 1991)

	Cardiology only		*Major interest*		
Year	*Adult*	*Paediatric*	*Adult*	*Paediatric*	*Total*
1992	1				1 (1)
1995	1				1
1997	1				1 (1)
1998					(1)
1999			1		1
2001	1				1 (1)
2003		1	2		3
2004	2		2		4 (4)
2005	2				2 (2)
2006	2				2
2007			1		1
2008			1		1
After 2010	4	1	2		7
Totals	14	2	9	0	25

Years omitted: no retirements expected.

towards early retirement, the complete data do show a trend similar to that in England and Wales.

Table 8 shows Health Districts without cardiologists in England and Wales. Much interest always centres around the number of Health Districts with only minimal provision for cardiological services. We believe that every Health District should have at least one individual trained in the specialty and working at least 40% of professional time within it. This is important not only for the time that the cardiologist can spend in service work, but also for the benefit of the influence that will extend to other staff members and to the training for junior medical staff whatever their medical specialty. In this report we have distinguished between the Health Districts that have fewer than seven sessions (sometimes only two or three sessions provided by a visiting cardiologist) and those that have no physician who meets our modest criteria. The picture is gloomy: in the 12 months since the last survey none of the Health Districts acquired a cardiologist. Three Districts fall into this category for the first time—designated in the table as "losses". Two of these were real but only because of sessional changes. The other represented a previous error. There were, however, no losses in terms of individuals. The previous report stated that 31 Districts were "completely without" cardiology, but that did not take account of seven Districts that have occasional visits, and a few others may not have declared them in previous surveys. Nearly nine million people live in Districts without adequate provision for cardiology. This figure has increased slightly since the last survey. The position of Wales is complex because the nine Health Districts have between them 18 district general hospitals. We do not have population figures for the individual hospitals, but a total of 10 of them are without adequate cardiology. (Thus the data for Wales are not strictly comparable with those for England, and the position is worse than the data by Health District imply).

Table 9 shows comparable data for Scotland. Few hospitals within these Boards have even minor provision from visiting cardiologists. We have no table for Northern Ireland, but three hospitals had no separate provision. In these hospitals, however, the arrangements for cover were unusually good.

STAFFING: SENIOR REGISTRAR GRADE

Table 10 compares the numbers of cardiovascular physicians in each Region of England and Wales with the number of senior registrars and equivalents in post. Overall, the ratio of consultants to senior registrars is 5·9:1. There are no wide discrepancies in the ratios: the figure is smallest for Oxford, which has only eight Health Districts, and highest for South Western Region. Three of the senior registrar posts and six of the consultant posts shown in this table were vacant on the survey date but they have been included because the vacancies were shortly to be filled.

Our allocation from the Joint Planning Advisory Committee (JPAC) is 60 posts for adult and paediatric cardiology, of which 10 are "top-sliced" for a research allocation and two are top-sliced for the part time training of four individuals. The system for research allocation is bizarre and precludes effective planning. Each specialty is required to contribute towards a central pool from which posts are then made available for allocation by the Association of Medical Research Charities (including the British Heart Foundation) and by Regional Health Authorities. The allocation, however, is

Table 8 Health Districts without cardiology by Region of England and Wales (31 July 1991)

Region	*Population mid 1990*	*HDs*	*HDs with < 7 sessions*	*Losses*	*HDs completely without*	*Population with less than 7 sessions/HD*
East Anglia	2059·0	8	2 (2)			421·9
Mersey	2402·8	10	5 (5)		3	973·6
NE Thames	3802·9	16	3 (2)	1		726·6
NW Thames	3498·6	13	3 (3)		1	723·3
North Western	4016·1	19	5 (5)		4	869·6
Northern	3075·4	16	6 (6)		2	998·9
Oxford	2563·9	8				
SE Thames	3658·2	15	1	1		271·7
SW Thames	2978·6	13	3 (3)		1	736·8
South Western	3262·1	11	3 (3)		1	571·6
Trent	4704·5	12	3 (2)	1		636·6
Wessex	2940·3	10	2 (2)		1	251·4
West Midlands	5219·3	22	6 (6)			1036·1
Yorkshire	3655·7	17	3 (3)		2	490·9
Wales	2881·4	9	2 (2)		1	231·1
Special hospitals		4				
Totals	50 718·8	203	47 (44)	3	16	8940·1 (8305·3)

Table 9 Scottish Health Boards without cardiologists (31 July 1991)

Health Board	*Population without*
Borders	103·5
Fife	345·9
Forth Valley	272·1
Orkney	19·6
Shetlands	22·3
Western Isles	30·7
Total	794·1

not specialty specific. There is no guarantee that a specialty will receive back the same number of posts that have been contributed to the pool. Cardiology is called upon to make the largest contribution (10 posts) but the reason for this high number is historical and unclear. At the present time we have only four research posts allocated to us (included in the column labelled "supernumerary"), and we believe we had approximately the same number at the time of recent surveys. Thus in practice a quota of senior registrars is calculated and then subjected to a large and arbitrary "research" cut. We are required also to provide two posts for part time training, but as far as we know we have never used our complete allocation. We are close at the moment, with three individuals in post. Although we have never used our allocation, we were told at a recent JPAC review that it should be increased on the basis of our overall numbers, but fortunately our appeal against this decision was allowed. The system of "top-slicing" has kept our overall numbers below our allocation from 1984 to the present time. Our survey has uncovered an apparent anomaly: we have a total of 50 posts in the NHS and academic categories whereas our quota is 48, but this small difference does not compensate for the overall deficit.

Table 11 shows comparable data for Scotland and Northern Ireland.

Theoretically, the number of senior registrars completing their training period in any year should balance the number of consultant retirements, with a small correction for growth in the specialty based on historical data. Fluctuations from year to year would be expected unless the specialty were so large that variables cancelled out. In all of our surveys, however, we have seen appreciable deficits in consultant retirements in relation to the number of senior registrars expected to complete their training. For the five years 1992 to 1996 there should be 55 senior registrars available (including vacant posts) to fill only 34 posts, an excess of 21 senior registrars and lecturers (table 12). This figure does *not* cause us concern because we have seen a similar predicted excess in each survey, yet the relative dearth of trained senior registrars has remained unaffected or increased. The corresponding figure for 1990 was 17 and for 1988 it was 30. In this survey we have for the first time sought and included trainees in non-approved posts who do (or may wish to) compete for consultant cardiology vacancies. The 14 individuals who have been identified include some in other specialties such as clinical pharmacology. Many would have other avenues open to them. The phenomenon is not new but it has not been well recognised. We note that seven of 22 recent appointments were taken by individuals who were not in JPAC approved cardiology training posts. Without this supplement to our trainee numbers we would by now have faced a crisis. Further evidence of a dearth of senior registrars is provided by an examination of the length of time that consultants appointed in the 12 months *since* the survey date spent as senior registrars. Six had completed their four years training. But seven had completed less than four years, an additional seven had completed less than three years, and two more had completed less than two years training at the time of appointment. It is also clear from the data shown in table 12 that in July 1991 most of the senior registrars were due to complete their training from 1994 onwards, in other words they had been only recently appointed to the grade.

Tables 13 and 14 show comparable data for Scotland and Northern Ireland. The numbers for both are small but they suggest that the combination of new consultant appointments, earlier retirements, or deaths could very easily create an important negative balance in either of these countries.

Table 10 Cardiovascular physicians and senior registrars by Region of England and Wales (31 July 1991)

			Consultants			*Senior registrars*					
Region	*HDs*	*MCs*	*Cardiology only*	*Major interest*	*Total*	*NHS*	*Acad.*	*Supernumerary*	*Total WTEs*	*Total SR individuals*	*Ratio of consultants:SRs**
East Anglia	8	1	7	3	10	1		1 0	2·0	2	5·0
Mersey	10	2	9	6	15	3			3·0	3	5·0
NE Thames	16	3	15	9	24	3			3·0	3	8·0
NW Thames	13	2	17	7	24	3		1·0	4·0	4	6·0
North Western	19	3	13	11	24	3		0·5	3·5	4	6·0
Northern	16	1	12	9	21	2	1		3·0	3	7·0
Oxford	8	1	6	8	14	1	2		3·0	3	4·7
SE Thames	15	4	21	9	30	2	1	1·0	4·0	5	6·0
SW Thames	13	1	12	4	16	2			2·0	2	8·0
South Western	11	1	13	4	17	2			2·0	2	8·5
Trent	12	2	12	13	25	2	2		4·0	4	6·3
Wessex	10	1	6	10	16	2			2·0	2	8·0
West Midlands	22	3	18	15	33	2	2		4·0	4	8·3
Yorkshire	17	3	16	10	26	2	2		4·0	4	6·5
Wales	9	1	6	9	15	1	1	2·0	4·0	4	3·8
Special hospitals	4	4	30		30	7	1		8·0	8	3·8
Totals	203	33	213 (186)	127 (137)	340 (323)	38	12	5·5	55·5	57	5·9

*Individuals not WTEs.
Three of the SR posts shown were vacant on the survey date.

Table 11 Cardiovascular physicians and senior registrars in Scotland and Northern Ireland (31 July 1991)

	No of HBs	*No of MCs*	*Cardiology only*	*Major interest*	*Total cardiologists*	*Senior registrars*
Scotland	15	4	24	18	42	7
Northern Ireland	4	1	16	9	25	4

Figures for Northern Ireland include one SR vacancy.

Staffing: a statement of need

By any reasonable yardstick, the provision of cardiological services in the United Kingdom falls far short of a level that could be considered reasonable for an advanced country. While this is true of many specialties, cardiology has a unique claim: heart disease is by far the most important cause of premature mortality and is an important cause of morbidity at all ages. We have available the possibility of prevention, of medical treatment, of surgical treatment, and of rehabilitation. These facilities are not only poorly resourced but are often unavailable because of inadequate staffing levels. We appreciate that ideal levels of provision are unattainable and that a compromise is necessary. The target that was set out at the time of the Sixth Biennial Survey was modest. It called for 157 new consultant posts over a 10 year period. This is the minimum necessary for acceptable staffing levels in our cardiac centres and district general hospitals.

For the centres we need to provide sufficient cardiologists for the 500 coronary operations and the 250 angioplasties per million population per year recommended in the Fourth Joint Colleges Report[6]—this total falling well short of what would be required to deal adequately with the burden of coronary disease, particularly in the elderly whose requirement for interventional cardiology in the United Kingdom receives too little consideration.

For a district general hospital we require at least one trained cardiologist, and for populations of over a quarter of a million we require two. We emphasise that a growth of 5% per annum, which we have still not attained, could meet these twin objectives by the year 2000, but this makes no allowance for advances (such as arrhythmology which can be highly effective with a favourable cost-benefit ratio) nor does it go any way to correct the service load on senior registrars and registrars. Calls for shorter training programmes must recognise the special needs for practical experience in cardiology but no appropriate progress can be made while the contribution by trainees to service needs is so great and the time for structured teaching programmes by consultants is so constrained. Only an appreciable increase in senior posts can correct this unsatisfactory situation. We hope that the new demands from the internal market will help to stimulate the growth that is so urgently needed.

We are especially concerned that the number of Health Districts without adequate expertise in cardiology did not fall during the year since the previous survey. Where provision is particularly poor or even absent the pressure for improvement is restrained because the public, general practitioners, and even hospital consultants have little awareness of what can be provided.

Even if the new consultant posts that are needed are not created we face a crisis within the next three years because of a shortfall in senior registrar posts. The considerable expansion in cardiology that did take place 25 years ago was reflected in a stepwise near doubling of consultant opportunities from 1997 onwards. We have long been aware of this, but recently the situation has changed because of the move to earlier retirement so that now the increased requirement is somewhat less abrupt but starts from 1995—two years earlier.

The factors that we have to take into account in deciding the number of senior registrar posts that we require are complex. First we have to cater for an expected growth of 5% per annum (a figure that we have almost reached). Secondly, we have to prepare for the increased opportunities from retirements that will start shortly and continue indefinitely. Thirdly, we have to correct the current tendency for premature appointment to consultant posts—often occurring before three years at senior registrar level, and at the same time take note of the relatively large percentage of posts that are being filled by trainees who are not in approved cardiological posts. On the other hand a reduction in the length of senior registrar training from four years to three will provide some relief, at least theoretically (we recognise, however, that three years is already the average time in post). It is conceivable that part of our immediate shortfall may be met by hospital or departmental

Table 12 Contract expiry dates for senior registrars compared with retirement dates for consultants in England and Wales (31 July 1991)

Year	*Consultants retiring*	*Approved SRs available*	*Balance*	*(Other SRs competing)*
1992	7	4	−3	(1)
1993	3	9	6	(4)
1994	5	12	7	(1)
1995	10	16	6	(4)
1996	9	14	5	(4)
Totals	34	55	21	(14)

Table 13 Contract expiry dates for senior registrars compared with retirement dates for consultants in Scotland (31 July 1991)

Year	*Consultants retiring*	*Approved SRs available*	*Balance*
1992	1	2	1
1993		1	1
1994	1	1	
1995	1	1	
1996		2	2
Totals	3	7	4

Table 14 Contract expiry dates for senior registrars compared with retirement dates for consultants in Northern Ireland (31 July 1991)

Year	*Consultants retiring*	*Approved SRs available*	*Balance*
1992	1	1	
1993			
1994		1	1
1995	1		−1
1996		1	1
Totals	2	3	1

closures that some see as inevitable. We hope that redeployment (if it occurs) will be only a short-term phenomenon.

We are certain that we need an increase in senior registrar posts, but the complexities make accurate prediction of our requirement very difficult. We recommend as a first step the ending of the top-slicing of 10 posts for research. If a senior registrar or lecturer does go into research there can indeed be an increase in the trainee numbers at any one time, but averaged over the years the numbers entering the senior registrar/lecturer grade and the numbers leaving it are unaffected. The top-slice was therefore always illogical, and has served us poorly because few of the posts are taken up by trainees wishing to enter the specialty. We believe that these 10 posts should be distributed as soon as possible between approved NHS posts and lecturer posts, leaving our overall number of senior registrar/lecturer positions at the present level of 60. (Our data at present suggest that we do have an excess of two so the real "gain" may appropriately be eight posts.) Unfortunately the interval between JPAC approval and having an individual appointed is about two years, so it is inevitable that posts will continue to be filled by trainees from non-approved positions and from those in other specialties such as clinical pharmacology. We also believe that at this time of rapid change in service provision and in the pattern of training we need an annual review; without this we have little chance of matching trainees to future consultant opportunity with a balance that is in any way acceptable.

Future surveys and annual reports must also take note of registrar numbers, but calculations for this grade clearly depend upon sound planning at senior registrar and consultant levels.

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BRITISH CARDIAC SOCIETY

The future of paediatric cardiology in the United Kingdom

Report of a joint working party of the British Cardiac Society and the Royal College of Physicians of London

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Introduction

This committee was formed as a result of a perceived crisis in consultant staffing in paediatric cardiology in the United Kingdom. Though an imbalance between the numbers in training and the available consultant positions is probably endemic to the National Health Service (even with the Joint Planning Advisory Committee), the situation which confronted the profession in 1987 and 1988 was very worrying. Two newly constituted consultant posts in paediatric cardiology and two existing posts were unfilled because there were no suitably trained applicants.

The British Cardiac Society and the Royal College of Physicians set up this working party in 1988 to look at the causes of the problem and to make recommendations for the future. The working party took a wide view of its remit and recognised that the training needs of paediatric cardiologists and the projected numbers needed by the profession in the next ten years contributed to the problem.

Training of a paediatric cardiologist

(These recommendations are now incorporated into the Joint Committee on Higher Medical Training Guidelines 1989.) Paediatric cardiology is now practised almost exclusively in regional and supraregional centres with two or more consultant paediatric cardiologists and the supporting staff and equipment required to diagnose and treat cardiac conditions in children, most of which are congenital. Some, but not all such centres, are associated with general and other specialised paediatrics. It is essential that paediatric cardiologists have adequate training in paediatrics to allow care of the whole child. In addition, training is needed in the two growing areas of paediatric cardiology—care of the adolescent and adult with congenital heart disease and diagnosis and management of fetal cardiac abnormalities.

GENERAL PROFESSIONAL TRAINING

Before embarking on the specialised part of their training paediatric cardiologists will usually have obtained the MRCP or an equivalent qualification, either in paediatrics or in medicine. Training should include paediatrics or cardiology.

HIGHER SPECIALIST TRAINING

At some stage during an individual's training either general, professional or higher specialist, it is normally required that 6–12 months should be spent in adult cardiology and one to two years in paediatrics including six months in a neonatal unit, preferably a regional referral unit. Flexibility is accepted and expected. The normal training period for paediatric cardiologists should be increased from four to six years. At least four years should be in a specialist paediatric cardiological centre dealing with all forms of heart diseaser including neonatal and infant, and investigation of the fetal heart and circulation. Liaison with other paediatric specialties and adult cardiology should be encouraged during this period. Experience in the intensive care of paediatric cardiac surgical patients is essential. During the training period certain aspects of cardiology may need to be obtained by exposure to the adult branch of the specialty—for example, pacing, management of arrhythmias, exercise testing, and nuclear cardiology. Trainees should spend the equivalent of one year in cardiovascular research.

A joint group (under the chairmanship of Dr Douglas Chamberlain) representing the Specialty Advisory Committee and the Committee on Cardiology of the Royal College of Physicians of London and the British Cardiac Society has recently proposed a new scheme of training for adult cardiologists.[1] This consists of three years general professional training (senior house officer and registrar level), three years of high professional training at registrar level, and at least three years at senior registrar level. The working party's recommendations for paediatric cardiologists are not incompatible with these proposals although the current lack of registrar positions in paediatric cardiology in the United Kingdom presents an obvious problem.

The Association of European Paediatric Cardiologists is also studying the training of young consultants with a view to achieving some degree of unanimity by 1992. Preliminary information suggests that our recommendations would also fit with the European plan.

We recommend that paediatric cardiologists should have a minimum of three years general professional training after registration followed *by three years of higher professional training at registrar level and a further three years at senior registrar level. Ideally one year should be spent in research during this period.*

Previous reports on paediatric cardiological services

REPORT OF THE BRITISH PAEDIATRIC ASSOCIATION WORKING PARTY ON CARDIAC SERVICES FOR CHILDREN IN ENGLAND AND WALES

This unpublished report, prepared in February 1979 by O P Gray, T P Mann, M J Simpkiss, M C Joseph, R S Jones, and G H Watson, carefully documented the position in the 1970s. The report was concerned because there were too many small units that lacked the facilities essential for successful treatment of children with congenital heart disease. It emphasised that all staff should have paediatric training and particular expertise in handling the newborn. Improvements in ancillary services including specialist physiotherapy, social work, and parental accommodation were identified and recommended. Other improvements in invasive and non-invasive investigational services and provision of dedicated surgical theatres were identified and recommended.

This working party strongly advised that paediatric cardiology was better practised in a large children's hospital or in a children's department of sufficient size in a general hospital with the corresponding regional cardiac unit adjacent to the children's unit. Most of the centres in England and Wales fulfil one or other of these criteria. The British Paediatric Association's report recommended that there should be two major units in the London area and that there should be four large centres outside it to provide services for Bristol and Cardiff, Liverpool and Manchester, Leeds and Sheffield, and Birmingham. Geographical consideration suggested that Newcastle and Southampton should continue as separate smaller units.

Much of the philosophical content of the British Paediatric Association report is still important and appropriate. The major centres have by and large been suitably developed. A Welsh centre is shortly to be established to provide a total service for the children of South and Mid Wales. The service is likely to develop to provide adequate country wide cover.

THE SECOND AND THIRD REPORTS OF THE JOINT CARDIOLOGY COMMITTEE OF THE ROYAL COLLEGE OF PHYSICIANS OF LONDON AND THE ROYAL COLLEGE OF SURGEONS OF ENGLAND 1980[2] AND 1985[3]

These two reports examined the provision of overall cardiac services and staffing throughout England and Wales and dealt with paediatric cardiology as a part of this whole.

The second report used data from the New England Regional Infant Cardiac Programme and from the Joint Committee on Higher Medical Training and Joint Committee on Higher Surgical Training to make several recommendations, some of which are still appropriate today. The report argued strongly for specialisation in paediatric cardiac surgery with its increasing emphasis on correction in infancy. The skills needed should be concentrated in a few centres and supported by a central fund. The report also recommended that the needs of older paediatric cardiac surgical patients should be met within the same units. Each unit was to have two consultant cardiothoracic surgeons and two or three consultant paediatric cardiologists, all of whom would participate in the cardiological care of the younger and the older patients with congenital heart disease. Recognition as a supraregional centre was to be based not just on workload and geographical location but also on the quality of the work done. To date no real audit of surgical results is available and surgical needs are still based purely on the number of patients undergoing operation. The recommendations of the report for paediatric cardiology outside supraregional centres were vague and suggested some form of joint care by cardiologists and paediatricians.

The third report in 1985 perpetuated the separation of surgical care for patients under one year of age and patients over one year of age. The report referred to the recently endorsed and established nine supraregional centres in Birmingham, Bristol, Brompton Hospital, Great Ormond Street, Guy's Hospital, Leeds, Liverpool, Newcastle, and Southampton. The report suggests that there should be no more than nine centres. In choosing this figure the authors of the report obviously followed the Black Committee recommendations, which were partly based on a desire to improve standards but were also designed to limit the spread of the specialty and cut costs. The 1985 report recommended that such supraregional centres should also treat older children with heart disease. Supraregional centres were said to require a minimum of two surgeons to maintain 24 hour year round cover and between two and four paediatric cardiologists.

The reality of paediatric cardiological practice at the moment is a little different from the conclusions of the third report. The number of consultant paediatric cardiologists has indeed increased in the supraregional centres. But few supraregional centres have two full time paediatric cardiac surgeons. While the concept of supraregional funding for infant cardiac surgery is working well, the medical and surgical care of the older child and adolescent has not been planned nationally but has been left to chance development. The working party believes that we need a national plan to provide a service for this increasingly important group.

Paediatric cardiological services in the next decade

The British Paediatric Association working party in 1979 based its predication of future services on reports of the incidence of congenital heart disease from North America and Australia. They chose a figure of seven or eight per 1000 live births and there is no reason to believe that this figure will change in the near future. It will be a long time before prenatal diagnosis affects the number of patients with serious malformations who reach the paediatric cardiologist.

The present working party tried to estimate the caseload of paediatric cardiological centres to the end of the century based on population trends and predictions from the Department of Health. The method of prediction is not entirely clear and probably not entirely uniform throughout the United Kingdom. Several of the northern regions predict a 0–3% increase in the number of children under 14 years by the year 2001, whereas Wessex predicts an increase of up to 22%. Taking the predictions for the country as a whole there will be an increase in the total number of children under 14 years of between 9% and 10% by the year 2001. Assuming that the incidence of congenital heart disease remains static then the service will have to cope with a very considerable increase in patient load in the next decade.

At the present time there are *48 full time or maximum part time paediatric cardiological posts in the United Kingdom. Vacancy and retirement will necessitate consultant appointments being made to existing positions by the year 2001.* If this working party's recommendations for growth are accepted *then a further ten new posts will be required by 2001* (see recommendation [a]). Candidates for these positions must come at present from six senior registrar positions in the United Kingdom (two more have been provisionally agreed but not yet implemented). There is no infrastructure of middle grade registrar posts in paediatric cardiology to supply suitable candidates for these senior registrar positions. There are only three full time middle grade registrar posts in paediatric cardiology at the Hospital for Sick Children, Great Ormond Street, and one at the Royal Brompton National Heart and Lung Hospital. Nine further centres have one registrar who is part of either an adult cardiological or a paediatric rotation. Most of them will not become paediatric cardiologists.

The immediate shortfall in trained candidates for consultancies cannot be overcome by planning. On the other hand it was unrealistic to insist that senior registrars spend four years in training before being appointed to consultancies. Regional health authorities should be *encouraged to identify suitable though inexperienced candidates for proleptic appointments with secondment to other centres to complete their training.*

The existing posts for senior registrars may provide sufficient suitably trained applicants for existing consultancy vacancies during the 90s but they will not allow for any expansion. On the basis of increased consultant posts alone, therefore, an increase both in senior registrar and registrars is obviously indicated.

Factors affecting the workload patterns of paediatric cardiologists

Since the previous reports the specialty has undergone remarkable changes as a result of technological advances. Congenital heart disease is now diagnosed and treated in prenatal and in adult life in a way that was unthinkable two decades ago.

Specialists in adult cardiology are now more heavily committed to the treatment of ischaemic heart disease than ever before. They have neither time nor unfortunately the "know how" to cope successfully with the increasing number of adults with congenital heart disease. Accurate data on the case load of adult and adolescent patients with congenital heart disease are not at present easy to come by. While as many as 20 000 patients probably need cardiological supervision into adult life in the United Kingdom, an estimated 700 per annum with complex problems will require some form of cardiac surgery or intervention. The problem is bound to become increasingly important. Care of this group may fall to the paediatric cardiologist or to the specialist in adult cardiology with suitable experience. The most suitable choice will depend on the local situation. Services need to be planned centrally for the whole country. *The working party strongly believes cardiologists to treat this special group of patients should be trained in existing supraregional paediatric cardiological centres where expertise in adult cardiology is also available. Because few patients will be requiring active intervention supraregional funding arrangements would be appropriate.*

Interventional procedures are now commonplace in the treatment of congenital heart disease. Aortic valve stenosis, pulmonary valve stenosis, and coarctation and recoarctation of the aorta are all often well treated by means other than surgery as the first line of attack. *Despite the impact of non-invasive techniques, the number and complexity of invasive paediatric cardiological procedures are actually increasing and will continue to do so for the foreseeable future as interventional procedures become more commonplace.*

There is a trend for paediatric cardiological centres to be established as regional clinics. Because many of the regions are so large patients may have to travel 100 and more miles to the regional centre. It is usual for at least one of the paediatric cardiological team to be out of the regional centre attending a peripheral clinic every week. *The peripheral clinic needs to be built into job descriptions and the implications for staffing numbers needs to be considered.*

Prenatal diagnosis, as pioneered at Guy's Hospital, is fast becoming part of the everyday work of the regional and supraregional paediatric cardiological unit. It is time consuming and technically difficult. Realistically only the paediatric cardiologist has the knowledge to use the information that prenatal diagnosis gives to advise on the continuation or termination of pregnancies when congenital heart disease is diagnosed in the fetus. *The working party strongly believes that this new discipline must be recognised as part of the work of a paediatric cardiologist.* The specialist nature of the scanning and counselling means that it is a regional or supraregional centre activity and ought to be funded on a supraregional or regional base by protected funds.

Recommendations

The recommendations that follow are based on existing work patterns and population predictions. *If the implications of "Achieving a Balance" are ever realised then the staffing requirements of the specialty would be significantly increased even over the changes suggested in this document.* At present, paediatric cardiological centres, whether supraregional or regional, serve populations of on average three million people. For historical reasons some of the larger centres serve more than five million people. It is impossible to assess the true population drained by the London centres because of their local situation and referral patterns.

(*a*) Building on recommendations of the other working parties, this committee acknowledges the change and growth in the work patterns and caseload of the paediatric cardiologist and recommends a minimum of *one consultant paediatric cardiologist per million of the population.* This means that no unit should have less than three consultants, bringing the speciaty into line with general Department of Health recommendations at present applied to other grades of hospital doctor. The working party thinks that this recommendation is of great importance in a consultant orientated specialty such as paediatric cardiology. The implications of this recommendation in terms of future new jobs are considerable. The total number of posts throughout the United Kingdom will rise from 48 (41 existing posts in England and Wales, two in Northern Ireland, and five in Scotland) to between 55 and 60.

(*b*) This increase in consultants cannot possibly be filled from existing senior registrar posts and the working party therefore recommends that *every supraregional centre should support a senior registrar training post and at least two middle grade registrars full time in paediatric cardiology.* An increase of at least three senior registrars is needed. Two such posts have been provisionally agreed by the General Purposes Sub-Committee 1990 of the Joint Planning Advisory Committee. The working party believes that the provision of middle grade registrar posts is crucial to the provision of suitable experienced candidates to fill the senior registrar posts.

(*c*) The working party acknowledged the usefulness of supraregional arrangements for funding infant cardiac surgery in existing centres. This problem has been addressed and largely solved. Now the profession and central planners need to recognise the vital expansion of paediatric cardiology into prenatal and young adult life. *These developments are as important as infant cardiac surgery and need careful central planning and protected funding.*

Summary

(1) The working party has considered the requirements for the training of paediatric cardiologists and has suggested a flexible curriculum that allows the specialty to benefit from doctors coming into it from both adult cardiological and paediatric disciplines.

(2) The working party appreciates that the short term problem with appointment of paediatric cardiologists cannot be solved immediately and recommends that appointing authorities should show patience. They should look to the possibility of identifying suitable candidates, at present in training, and making proleptic appointments to allow appropriate training to be completed.

(3) There is a need for an increase in the number of paediatric cardiologists to service the specialty during a period when the patient load will increase because of population trends and changes in work patterns (specifically adults with congenital heart disease and prenatal cardiology). The care of adults with congenital heart disease has to be planned, certainly at regional and probably supraregional levels, and the financial and training implication has to be recognised.

(4) The working party therefore recommends that there should *be one consultant paediatric cardiologist per million* of the population to allow for these changes in the service.

(5) The working party considers that this report makes a very strong case for an increase in the number of senior registrar and registrar posts in the specialty. The existing number of junior posts will not fill the increase in agreed new posts and those made vacant by retirements between now and the end of the decade. When the additional posts recommended by the working party are taken into account *at least three new senior registrar posts are needed.* To make sure that a satisfactory supply of experienced candidates is available to fill the senior registrar posts the working party *recommends the provision of two full time middle grade registrar jobs for each senior registrar position.*

1 Joint Training and Manpower Group representing the Specialty Advisory Committee and the Cardiology Committee of the Royal College of Physicians of London, and the British Cardiac Society. Proposals for a new training programme for cardiology. *Br Heart J* 1990;63:317–20.
2 Second report of a Joint Cardiology Committee of the Royal College of Physicians of London and the Royal College of Surgeons of England on combined cardiac centres for investigation and treatment with a note on the requirements of cardiology in hospitals outside such a centre. *Br Heart J* 1980;43:211–9.
3 Third report of a Joint Cardiology Committee, Royal College of Physicians of London and the Royal College of Surgeons of England. Provision of services for the diagnosis and treatment of heart disease in England and Wales. *Br Heart J* 1985;53:477–82.

Br Heart J 1992;68:634–6

LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

Limitations of transoesophageal echocardiography in patients with focal cerebral ischaemic events

Sir—In their study of patients with focal cerebral ischaemic events, de Belder and colleagues[1] showed that transoesophageal echocardiography confirmed the findings of transthoracic echocardiography and detected additional abnormalities. In each case the transthoracic echocardiography was performed before transoesophageal echocardiography. The echocardiograms were interpreted by someone who had not been involved with imaging and who was blind to clinical information. Was the person who reported the transoesophageal echocardiogram blinded to the result of the transthoracic echocardiogram? Was the transoesophageal operator also blinded to the transthoracic result? A lack of blinding might mean that the transoesophageal operator would try harder to demonstrate a lesion he knew to be present and the transoesophageal reporter would look harder to find a lesion he already knew to be present from the transthoracic echocardiogram. While this would mimic the clinical situation it does not tell us anything about the relative sensitivities of the two techniques which can only be determined if the results from each technique are obtained entirely blind to the results of the other.

The main difference between transoesophageal and transthoracic echocardiography in this study was that transoesophageal echocardiography picked up more right-to-left shunts (23% *v* 7%). Was this failure to demonstrate by transthoracic echocardiography two thirds of the shunts, which seem to be present, the result of their technique? Others using more aggressive protocols and transthoracic echocardiography have shown an incidence of shunts in healthy individuals similar to that found by de Belder *et al* with transoesophageal echocardiography.[2,3] Alternatively could it be that the shunts found by de Belder *et al* by transthoracic echocardiography were larger (both anatomically and functionally) and therefore the ones most likely to have implications for aetiology of cerebral ischaemic events in their patients?

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1 de Belder MA, Lovat LB, Tourikis L, Leech G, Camm AJ. Limitations of transoesophageal echocardiography in patients with focal cerebral ischaemic events. *Br Heart J* 1992;67:297–303.
2 Wilmshurst PT, Byrne JC, Webb-Peploe MM. Relation between interatrial shunts and decompression sickness in divers. *Lancet* 1989;ii:1302–6.
3 Cross SJ, Evans SA, Thomson LF, Lee HS, Jennings KP, Shields TG. Safety of sub-aqua diving with a patent foramen ovale. *BMJ* 1992;304:481–2.

Sir—de Belder *et al* make the point that transthoracic and transoesophageal echocardiography may have a limited role in the evaluation of patients with transient ischaemic attacks and stroke. Though their analysis of the echocardiographic findings referable to the heart was thorough, they did not rotate the transoesophageal echocardiography probe towards the thoracic aorta. So they did not identify raised plaques with superimposed thrombus in the aortic arch, which are an important factor in patients with neurological events. In 1990 we reported three patients who had emboli in whom such raised thrombotic plaques were seen on transoesophageal echocardiography,[1] and the following year we showed in a case-control study that these lesions are associated with cerebral and peripheral embolic disease.[2] Others have reported this association too.[3,4] A large necropsy study has found ulcerated plaques in the aortic arch of patients dying from stroke, in the same area as that in which raised thrombotic plaques (which may have mobile components indicative of superimposed thrombi) are seen on transoesophageal echocardiography.[5] In a recent analysis, we found that rather than being of limited use, the most important advantage that transoesophageal echocardiography has over transthoracic echocardiography in patients with embolic disease is the ability to diagnose raised thrombotic plaques in the thoracic aorta.[6] Therefore we think that transoesophageal echocardiography is indicated in all patients with otherwise unexplained embolic disease, and it may even have a role in the evaluation of patients with strokes of other presumed aetiology.

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1 Tunick PA, Kronzon I. Protruding atherosclerotic plaque in the aortic arch of patients with systemic embolization: a new finding seen by transesophageal echocardiography. *Am Heart J* 1990;120:658–60.
2 Tunick PA, Perez JL, Kronzon I. Protruding Atheromas in the Thoracic Aorta and Systemic Embolization. *Ann Intern Med* 1991; 115:423–7.
3 Pop G, Sutherland GR, Koudstaal PJ, Sit TW, de Jong G, Roelandt JR. Transesophageal echocardiography in the detection of intracardiac embolic sources in patients with transient ischemic attacks. *Stroke* 1990;21:560–5.
4 Karalis DG, Chandrasekaran K, Victor MF, Ross JJ, Mintz GS. The recognition and embolic potential of intraaortic atherosclerotic debris. *J Am Coll Cardiol* 1991; 17:73–8.
5 Amarenco P, Duyckaerts C, Tzourino C, Hénin D, Bousser M-G, Hauw J-J. Prevalence of ulcerated plaques in the aortic arch in patients with stroke. *N Engl Med J* 1992;326:221–5.
6 Tunick PA, Kronzon I. The improved yield of transesophageal echocardiography over transthoracic echocardiography in patients with neurologic events is largely due to the detection of aortic arch protruding atheromas. *Echocardiography* 1992;9:491–5.

These letters were shown to the author, who replies as follows:

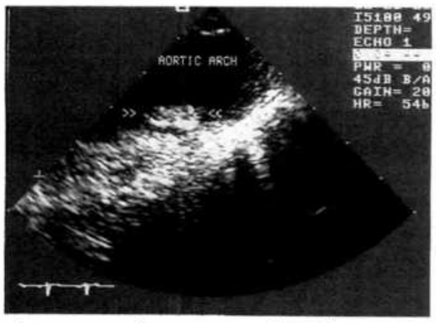
Sir—Peter Wilmshurst reminds us about the care needed in determining the relevant sensitivities of different echocardiographic techniques. Some of our patients underwent both precordial and transoesophageal echocardiography at the same visit. The studies were recorded on video tape and were thereafter reported by the individual who was blinded to the clinical details of the patients. In all instances, the precordial study was reported first. Dr Wilmshurst is correct in stating that the interpreter of the transoesophageal studies would not have been blinded to the interpretation of the transthoracic result in these cases. We do not believe, however, that the interpreter tried harder to detect abnormalities in those patients in whom the transthoracic study had already demonstrated them.

We do not believe that poor technique led to the low transthoracic pick-up of right-to-left shunts in these patients. Indeed, four to six precordial contrast studies were performed before a patient was defined as having no shunt. These were a mitral valve level M mode study and an apical four chamber or subcostal cross sectional study (and in many cases both), all of which were done before and during a Valsalva manoeuvre. We agree with the suggestion that the less common larger shunts, related to what Thompson and Evans referred to as "pencil" patency (as opposed to "probe" patency) of the foramen ovale[1] may be more likely to give rise to paradoxical embolic events. It may be that these are the shunts that are detectable from the precordium. These hypothetical thoughts are difficult to prove because there are no means of determining the size of a patent foramen ovale in vivo, nor of accurately determining the size of the associated (and variable) shunt.

The point of our paper, however, was not to give accurate data on the relative sensitivities of precordial and transoesophageal echocardiography in these patients. Given the drawbacks of precordial echocardiography that are overcome with the transoesophageal technique, it should be no surprise to anyone that the transoesophageal technique detects more abnormalities. This has now been demonstrated in numerous studies. Our point was that many of the abnormalities came as no surprise with the major exception of right-to-left shunts. Moreover, until we have some proven treatments to minimise recurrence rates when a patent foramen ovale or spontaneous contrast echoes are detected, we believe that the detection of such abnormalities may be of little value for the patient.

Paul Tunick and Itzhak Kronzon are wrong in assuming that we did not scan the aorta in our patients. We did—in all cases. We acknowledge their work on the possible relevance of raised thrombotic plaques in the aortic arch. However, in their initial series of three case reports,[2] case 1 was in atrial fibrillation and they cannot be sure that the cerebral event was related to the aortic lesion. In addition, the figure showing the lesion in case 1 was taken from the distal part of the arch; it is difficult to see how an embolus from this area would lodge in a cerebral vessel. Case 3 had severe carotid disease as well as the aortic lesion.

Tunick *et al* in a more detailed case-control study[3] provided rather more convincing evidence that raised thrombotic plaques in the aortic arch are associated with embolic



A transverse plane transoesophageal echocardiogram showing a protruding mass consistent with an atheromatous plaque in the middle part of the aortic arch. This was the only abnormality detected that could explain a recent cerebrovascular event.

events. However, their study was limited by the inclusion of patients with peripheral embolic events, by the lack of data on the size, morphology, and exact position of the atheromatous plaques and because they compared their cases with controls with cardiac disease. In addition, the sensitivity of the transoesophageal technique for aortic arch disease is unknown. Their data were, however, suggestive of a genuine association between the aortic arch lesions and cerebral embolism, although they do not demonstrate cause and effect. We recently performed transoesophageal echocardiography on a 57 year old man with no obvious cause of a stroke, in whom the only abnormality was a protruding plaque in the middle part of the arch (fig). However, such a gross abnormality was not seen in the patients reported in our recent study. We did see evidence of much less dramatic aortic arch atheroma in a few of these patients, but not in enough of them to convince us of its pathogenic relevance, and usually the patient had clinical or carotid ultrasound evidence of diffuse atheromatous disease. We have seen other patients with a peripheral embolic event who had clear evidence of protruding and mobile thrombotic plaques in the descending aorta. We agree with Tunick and Kronzon that these abnormalities would not be detected by precordial echocardiography and are worth seeking. We still, however, have no data on optimum treatment for such patients. Although Tunick *et al* have, somewhat radically, removed a protruding plaque in one patient,[4] this treatment cannot be recommended for all such patients.

Transoesophageal echocardiography did show interesting abnormalities in these patients that cannot be detected by conventional precordial echocardiography. However, it may not be possible to demonstrate anything more than an *association* of certain abnormalities with clinical events. The accumulating data on the patency of the foramen ovale, spontaneous contrast echoes, and atheromatous aortic disease do suggest a possible pathogenic role for these features in embolic events. We should now use this technique to evaluate treatments that might reduce the recurrence rate of embolic events in these patients.

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1 Thompson T, Evans W. Paradoxical embolism. *Q J Med* 1930;**23**:135–50.
2 Tunick PA, Kronzon I. Protruding atherosclerotic plaque in the aortic arch of patients with systemic embolization: A new finding seen by transesophageal echocardiography. *Am Heart J* 1990;**120**:658–60.
3 Tunick PA, Perez JL, Kronzon I. Protruding atheromas in the thoracic aorta and systemic embolization. *Ann Intern Med* 1991;115:423–7.
4 Tunick PA, Culliford AT, Lamparello PJ, Kronzon I. Atheromatosis of the aortic arch as an occult source of multiple systemic emboli. *Ann Intern Med* 191;**114**:391–2.

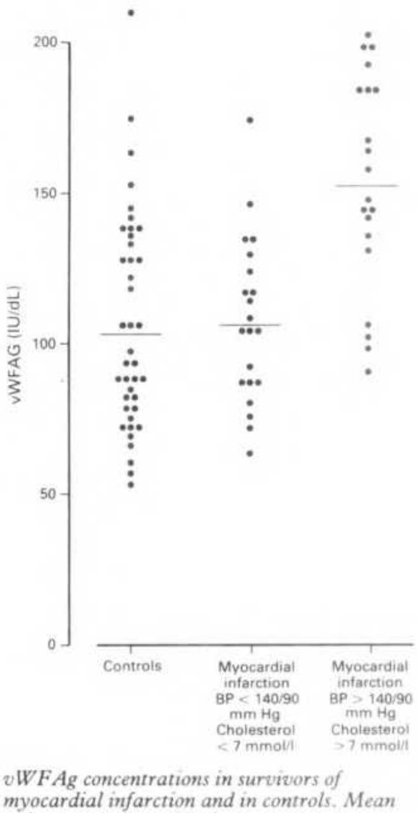
von Willebrand factor in plasma: a novel risk factor for recurrent myocardial infarction and death

SIR—Raised concentrations of von Willebrand factor antigen (vWFAg), a specific product of the endothelium) reflect damage to the endothelium. Jansson *et al* (*British Heart Journal* 1991;**66**:351–5) reported that high concentrations of vWFAg are present in ischaemic heart disease and predict reinfarction and mortality in survivors of myocardial infarction. Among the 123 survivors entering their study there were 88 cases of hypertension, diabetes mellitus, and smoking. Furthermore, the mean cholesterol concentration was 7 mmol/l, indicating hypocholesterolaemia in an unspecified number of patients.

Jansson *et al* point out that increased concentrations of vWFAg are found in diabetes mellitus. In the absence of symptomatic vascular disease, however, hypertension, hypercholesterolaemia,[1] and smoking[2] also act independently to increase vWFAg. We therefore asked whether vWFAg would still be increased in ischaemic heart disease once these risk factors for atherosclerosis were considered.

We studied 41 non-diabetic patients (mean age 59) six weeks after myocardial infarction (proven by a raised creatine kinase over 130 units/l with retrosternal chest pain typical or electrocardiographic changes or both. Twenty one of them said that they were current smokers, or smoking at the time of infarction, or had stopped in the year before infarction. Symptom free age and sex matched controls who were normotensive and normolipaemic were recruited from individuals attending hospital for endoscopy or repair of varicose veins. Resting systolic and diastolic blood pressures (SBP, DBP) were recorded, and blood was taken for routine measurement of cholesterol and vWFAg (by ELISA). For statistical analysis we used the Mann-Whitney and Spearman's methods on Minitab. Both cholesterol (mean (SD)) 6·3 (0·9) mmol/l, $p = 0{\cdot}0001$) and vWFAg (130 (39) IU/dl, $p = 0{\cdot}0004$) were higher in patients than in controls (5·2 (0·9) mmol/l and 104 (37) IU/dL respectively), confirming the work of Jannson *et al*. SBP and DBP were not increased in the patients with ischaemic heart disease but the values did correlate with vWFAg (SBP $r = 0{\cdot}34$, $p = 0{\cdot}033$; DBP $r = 0{\cdot}59$, $p = 0{\cdot}0001$). vWFAg did not correlate with cholesterol.

A subgroup of 20 patients (12 smokers) with ischaemic heart disease also had hypertension ($n = 10$, blood pressure >140 *and* >90 mm Hg) or a raised cholesterol concentration ($n = 10$, >7 mmol/l) at re-examination six weeks after discharge from hospital. The remaining 21 patients (12 smokers) were free of these risks. When these two groups were compared we found that those with either of these risk factors had significantly raised blood pressure (136 (18)/84(10) mm Hg) and cholesterol (6·8 (0·8) mmol/l). vWFAg was also higher (153 (35) IU/dl) than in the patients without these risks (107 (28), $p = 0{\cdot}0002$), which in turn was not higher than in the symptom free controls (figure).



vWFAg concentrations in survivors of myocardial infarction and in controls. Mean values are indicated by bars.

Although vWFAg is generally raised six weeks after myocardial infarction, in many cases this may be because of hypertension or hypercholesterolaemia or both. The presence or absence of smoking did not influence vWFAg concentrations in any group. We suggest that survivors of myocardial infarction without risk factors for atherosclerosis may have minimal evidence of damage to their vasculature. Conversely, in those with risk factors the endothelial insult is maintained and such patients may be at risk of further cardiac events. It would be instructive to learn whether Jansson *et al* could confirm this by performing multivariate analysis in the patients in their study.

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1 Blann AD, Miller JP, Waite M, McCollum CN. Endothelial cell injury in the risk factors of atherosclerosis. *Br J Surgery* 1992: (in press).
2 Blann AD. Increased circulating levels of von Willebrand factor antigen in smokers may be due to lipid peroxides. *Med Sci Res* 1991;**19**:535–6.

This letter was shown to the author, who replies as follows:

SIR—Blann *et al* report that in a case-control study they found higher concentrations of von Willebrand factor antigen (vWFAg) in survivors of myocardial infarction than in controls. Our study on survivors of myocardial infarction was prospective and showed that high concentrations of vWFAg predicted an increased risk of reinfarction and cardiovascular mortality in univariate Cox regression analysis.

In Blann *et al's* study only the subgroup of subjects with myocardial infarction and hypertension or raised cholesterol (and not the subgroup without these risk factors) had higher concentrations of vWFAg than controls. In Table 4 in our paper (*British Heart Journal* 1991;66:351–5) the results of multivariate Cox regression analysis demonstrate that the association between high concentrations of vWFAg and reinfarction or cardiovascular death was independent of these and other risk factors.

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Thallium scans in syndrome X

SIR—In their interesting retrospective study, Tweddel *et al* (*British Heart Journal* 1992;68:48–50) identified 100 patients with typical angina and normal coronary arteriograms (syndrome X). Thallium defects were found in 98% of the patients leading the authors to conclude that microvascular angina is commoner than generally appreciated. However, this conclusion must be treated with some scepticism because of work-up bias which commonly undermines claims for the diagnostic value of non-invasive testing in studies of this type.[1] Thus we are told that it is the practice at the Royal Infirmary, Glasgow to use the thallium scan as a screening test to select patients for angiography. Preferential selection of patients on this basis itself ensures a high prevalence of abnormal scintigrams in the 10% of their patient population with normal coronary arteries. Only if selection for angiography were independent of the results of thallium imaging could firm conclusions be drawn about the role of microvascular angina in syndrome X.

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[1] Kottler TS, Diamond GA. Exercise thallium-201 scintigraphy in the diagnosis and prognosis of coronary artery disease. *Ann Intern Med* 1990;113:684–702.

SIR—Connoisseurs of the circular argument will find few better examples than that recently presented by Tweddel *et al.* They contend that the finding of a high incidence (98%) of abnormal thallium scans in a retrospective study of patients with angina and normal coronary arteries is indicative of a high prevalence of microvascular disease. Unfortunately this contention is completely invalidated by their own admission that abnormal thallium scans were used for the selection of such patients for angiography in the first place. This being the case, it is surprising that the incidence of abnormal scans was not 100%.

The authors fail to document the number of patients seen with angina during the period under study who had normal thallium scans and as a consequence did not proceed to angiography. Thus it is impossible to estimate a possible lower limit for the true incidence of abnormal scans in such patients.

The assertion that the scan abnormalities detected represent microvascular disturbances is entirely speculative. Very few such patients have true myocardial ischaemia (reflected by lactate production on stress testing).[1] Indeed, the inability to demonstrate a correlation between severity of the scan defect and limitation of exercise capacity seems to indicate their lack of functional significance. On the contrary, as only 30% of the study patients had abnormal exercise tests the primary conclusion from this study must be the poor positive predictive accuracy and specificity of abnormal thallium scans for detecting significant coronary artery disease where the exercise electrocardiogram is normal.

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[1] Greenberg MA, Grose RM, Neuberger N, Silverman R, Strain JE, Cohen MV. Impaired coronary vasodilator responsiveness as a cause of lactate production during pacing-induced ischemia in patients with angina pectoris and normal coronary arteries. *J Am Coll Cardiol* 1987;9:743–51.

These letters were shown to the author, who replies as follows:

SIR—A more thorough reading of our paper would have shown that we were of course careful to emphasise that our unit's general practice of using positive thallium tests as a pre-catheterisation screening test inevitably determines that a very high proportion of our patients have positive thallium tests. Our study was not, did not intend to be, and could not have been an epidemiological study. It set out to provide a description of thallium test findings in an otherwise unselected group of patients presenting with typical effort angina and entirely normal coronary arteriograms. These patients with normal arteriograms represented about 10% of all those undergoing coronary arteriographic investigation in our unit, a proportion that is not grossly different from general experience where thallium is not used as a pre-screening test. Our finding that 98% of these patients showed abnormal thallium tests thus at least suggests—we claimed no more—that abnormal thallium tests are not uncommon in such patients and indeed might be found, by extrapolation, in some 5% of patients undergoing diagnostic coronary arteriography in other units unless our population is very peculiar. We were of course also careful to emphasise that an abnormal thallium does not necessarily imply reduced perfusion, or "microvascular angina" (one current word for the cardiologist's syndrome X in our continuing state of uncertainty) since it might also reflect abnormal potassium handling by the myocyte. Exercise tests and lactate production are recognised as having limited sensitivity in diagnosing ischaemia. Gold standards are hard to find in this arena.

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BOOK REVIEWS

Atrial fibrillation. J Rawles. (Pp243; £49.50) Berlin, Heidelberg, New York: Springer-Verlag, 1992. ISBN3-540-19699-4.

Atrial fibrillation is the commonest of all chronic sustained arrhythmias and until recently there was little to add to the early descriptions. The past decade has seen significant advances, with confirmation of the circus movement hypothesis. The other major development is in the understanding of how the atrioventricular node influences the ventricular response. Simple conduction of a proportion of the impulses from the fibrillating atria has been disputed by others in the past, and Rawles now adds his voice and (very usefully) his mathematical model to explain the behaviour of the atrioventricular node as an oscillator. Is this all too abstruse and too basic for the practising clinician? By no means: this slim volume deserves the attention of all cardiologists.

This is the work of one author. Some of the mathematical aspects are difficult, but they are worth studying and you will see that the explanations are quite clear. From them, phenomena such as concealed conduction and therapeutic regularisation of the ventricular rate are now easier to understand in logical terms.

The author's own interest in the changes in the cardiac output that occur during atrial fibrillation are carefully explained, on the basis of the use of non-invasive measurements and with the promise of further and better understanding with the continued use of Doppler techniques. The causes, ways of presentation, and treatment are all discussed, but more in terms of understanding than as a "cook book" list. What is particularly helpful is the bibliography. This is not just an accumulation of references haphazardly collected but rather a set of articles cited at the end of each chapter, each one having precise relevance to statements made in the text. This alone makes the book an important contribution.

While the clinical section is comprehensive it is rather tightly written. Why do coronary artery disease and myocardial infarction each have a subsection, yet lone atrial fibrillation and the sick sinus syndrome do not? The omission of any mention of the syndrome of alternating bradycardia and tachycardia is a surprise in a book written in Aberdeen. The role of chronic bronchitis, previously commonly believed to be important, also deserves more attention and a section of its own.

The discussion on drug actions is relevant with understandably considerable emphasis on what is known about the way in which digitalis works. Others will have to do more work on the mode of action of calcium antagonists before the author can give them corresponding depth of treatment, but what he says about each group of agents is ample and appropriate. He mentions also the use of techniques of ablation and considers carefully the need for prevention of embolic stroke and the ways in which this can be done.

John Rawles has provided us with an extremely useful addition to our knowledge, and his book on atrial fibrillation is one that I would strongly recommend. I think it should be in all medical libraries as well as in all departmental libraries in cardiology units. Quite apart from this, it is useful reading for all cardiologists, and certainly required reading for any who espouse an interest in cardiac electrophysiology.

DENNIS KRIKLER

Geriatric cardiology Edited by David T Lowenthal (Pp 263; £54.) London: Williams and Wilkins, 1992. ISBN 080365 6534

This short book, one of the *Cardiovascular Clinic Series*, brings another contribution to the burgeoning field of old age cardiology. Elderly patients with heart disease present special diagnostic and treatment challenges, because other vital organs may exhibit changes associated with ageing, wear and tear, and often disease. Some diseases occur only in old age: senile cardiac amyloidosis and conduction system degeneration to name but two. Lifestyle, socioeconomic and quality of life considerations often play a more important part in therapeutic decision-making in older people than they do in the young, and cardiologists need to have a grasp of some of the more important principles of geriatric medicine if they are to treat their elderly patients optimally.

Geriatric Cardiology is principally written by American cardiologists with some contributions by those from other disciplines. It is divided into four sections: epidemiology and clinical, therapy, and socioeconomic considerations.

The first section has a good short review of demography in the United States and a summary of the risk factors for cardiovascular disease by Dr Kannel in his usual inimitable style. The description of the ageing process in the heart is short but reasonably comprehensive and well-illustrated by line drawings, graphs, and tables in the second section.

In the third section the chapter on hypertension addresses the difficult problems that are encountered in evaluating the need for treatment in elderly people, but does not give any clear guidelines about treatment regimens. It seems to underestimate the importance of angiotensin converting enzymes in relation to calcium channel and β blockers in this age group.

The chapter on myocardial infarction emphasises the significance of this condition when it occurs without pain and quotes extensively from Pathy's work. However, those of us who deal extensively with acute geriatric emergencies are usually rather less impressed by the apparent absence of chest pain as one of the main presenting symptoms of acute myocardial infarction. There is a lack of balanced reports on the presentation of this condition in elderly people. It may well remain so while developed countries adopt such widely differing and disintegrated ways of managing acute medical emergencies in elderly people.

Valvar heart disease, cardiomyopathies, pericarditis and heart failure are well documented and there are excellent reviews on these subjects. The chapter on arrhythmias is reasonably comprehensive, although the effectiveness of permanent cardioversion in atrial fibrillation, by chemical or electrical means, is overemphasised. There is no discussion of the potential dangers of atrial fibrillation as far as thromboembolism is concerned. A more comprehensive discussion on the indications for, and type of, permanent pacemakers would have been welcome.

The chapters on drug therapy, intervention therapy for coronary heart disease, and cardiac surgery are well balanced and comprehensive. They reflect the increasingly aggressive line that physicians should adopt towards coronary and valvar diseases in elderly patients when they uncomplicated by other significant ageing processes or disease. The chapter on rehabilitation and lifestyle modification is excellent and underlines the growing enthusiasm in this area—one about which we shall doubtless hear much more in the future.

The final section has two chapters on socioeconomic and ethical considerations and these are welcome in any modern text. They given considered reviews—albeit with a North American perspective—of the problems that are rightly attaining ever greater prominence in the health care systems of developed countries. Perhaps is is nit picking to highlight the sudden appearance in the final stages of the text of the word "elders" when previously they had been "elderly", "old people", or "the aged", but this is one of the disadvantages of a multi-authored book in which 95% of the contributors are physicians.

Generally *Geriatric Cardiology* is a welcome contribution to books on heart disease in old age. It is also well presented, illustrated, referenced, and indexed and thus deserves a place on the bookshelves of all British hospital libraries, but priced at £54.00 few doctors are likely to buy it themselves.

ANTHONY MARTIN

A primer of molecular biology. R Roberts, J Towbin, T Parker, R G Biers. (Pp202; $49) New York: Elsevier, 1992. ISBN 0444 01657-0.

Few would argue against the view that the techniques now available in molecular biology have, and will continue, to advance our understanding of human cardiac disease. Most practising cardiologists have come to terms with the production of therapeutic substances such as plasminogen activator by recombinant DNA technology. Molecular biology has far more to offer in terms of diagnosis and understanding the basic mechanisms of disease. These aspects require a deeper knowledge of the principles of the technology, which are not always easy to acquire by those who do not practise the trade of molecular biology. Few clinicians will be totally conversant with northern, western and Southern blots and even the meaning of a lod score is not immediately obvious.

This primer first aims to bridge this gulf and then sets out to show how the techniques have been used to give an understanding of mechanisms in cardiac disease.

The first objective has been achieved extremely well. The role of nucleic acids and genes in the synthesis of proteins is well explained and illustrated by numerous line diagrams. Those who wish to know what Southern blots are will find the technique clearly explained and illustrated. There are lucid sections on the essentials of molecular genetics, the concepts of linkage and lod scores, and restriction fragment mapping in the isolation of genes.

The second objective of the book, to show how these techniques have been used, is less successful largely because it is incomplete. What is there is done well. There are chapters on the molecular biology of contractile filaments, myocyte growth and hypertrophy, and myocyte ion channels. Even within these sections, however, the clinician will find little help in understanding how the clinical picture is produced. Put another way, in the terminology of molecular biology, there is little discussion of the link between genotype and phenotype. For example, the abnormalities of heavy chain myosin are described but not how these might cause the disease of hypertrophic cardiomyopathy.

There are notable omissions. For example, there is no discussion of the genetic abnormalities of lipid metabolism or of connective tissue synthesis, thus familial hypercholesterolaemia and Marfan disease are not mentioned.

The authors no doubt believe, with some justification, that if the book were comprehensive in this regard it would be larger and more expensive.

For those who wish to understand the basic technology of molecular biology and to have some examples of its use, this book is an option. There are competitors in this market and potential readers should look around—but this book is both effective and relatively cheap.

MJ DAVIES

The title reviewed here is available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add £2 per item for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (MasterCard, VISA, or American Express) stating card number, expiry date, and your full name.

NOTICE

The 1993 Annual Meeting of the **British Cardiac Society** will take place at the Wembley Conference Centre from 18 to 21 May.

Br Heart J 1992;68:638–9

BRITISH CARDIAC SOCIETY NEWSLETTER

Health of the Nation

We have heard criticism that the British Cardiac Society did not make known to members its response to the government's green paper or to the strategy document that followed. Many Regions and Districts are now discussing implementation and have invited participation by cardiologists, and of course we welcome this. We can provide a copy of our response to any who may request it, but the following is a brief summary of some of our recommendations.

Prevention must have a major role in any health strategy. The society stressed that tobacco smoking is the major avoidable contributor to premature mortality from coronary heart disease, and urged that tobacco advertising should be phased out as soon as possible—in line with the policy adopted by other socially advanced countries. The specific roles for the government, the National Health Service, and health education and volunteer groups include the organisation of anti-smoking campaigns, advice on the risks of smoking and on techniques of quitting, the promotion of workplace anti-smoking policies, and the recognition of the relation between an increased price of tobacco and reduced tobacco consumption. We need better education of health professionals in food and nutrition so that sound advice can be given to the community, with an increased emphasis on schools and the workplace. In addition to a lower content of saturated fat in our diets, we need a higher intake of vegetables, fruit, and fish. There should be better facilities for exercise—with encouragement for adults to cycle or walk to work where it is practical to do so. Disease surveillance needs greater emphasis in England where the Department of Health failed to adopt the WHO MONICA project in the early 1980s.

The society emphasised the role of district general hospitals in the provision of cardiac care, and urged that all of them should have at least one well trained cardiologist in order to use effectively the recent technological advances for the diagnosis and treatment of heart disease. Rehabilitation and resuscitation needed more resources: they are relatively cheap with favourable cost-benefit ratios. At least four technicians are needed in district hospitals for every 250 000 population. These highly skilled supporting staff can be responsible for much of the routine work of a cardiac department. Within the major centres there should be sufficient cardiac catheterisation laboratories to provide for the number of patients who need investigation, and waiting lists should not be longer than six weeks. We believe that 600 bypass grafts per million population per year together with 400 angioplasty procedures would be modest provision for legitimate needs. These figures (which do not include those for valve surgery) would permit reasonable treatment of the elderly who are at present often excluded inappropriately on the basis of age. We believe that some 50% of the 300 pacemakers that are required per million population should have the facility of rate responsiveness. The routine waiting list for a pacemaker should not exceed one week. The provision of 40 implantable defibrillators per million population per year would enable treatment to be given to most younger victims of aborted sudden cardiac death, though we recognise that use of such units should be limited.

Many of these recommendations have not been reflected in the government's strategy document. But the proposals are modest and we believe that all members of the society would endorse them.

Read codes

We have discussed Read codes previously in September 1991 and in May 1992. Malcolm Towers who represents the specialty in the work to develop the codes has written to report progress. "The British Cardiac Society, with about 40 other specialty groups, was invited to review and expand existing Read codes. The specialty working group — a subsection of the Data Management Committee — has been set up under the chairmanship of John Parker. Other members are Peter Macfarlane (electrocardiography), Tony Rickards (electrophysiology and pacing), Robert Anderson (paediatric cardiology), Martin Rothman (intervention), Graham Leech (echocardiography), and Richard Underwood (nuclear cardiology). There is also a "general group" comprising John Birkhead, Michael Petch, Nick Boon, and Malcolm Towers. Cardiology was one of the early specialties to receive official approval and funding from the Centre for Coding and Classification in Loughborough. We are to have a special computer which will be set up in 9 Fitzroy Square. Good progress is being made especially in those areas where we are starting with a "clean sheet". We expect the general group to move forward when we have the computer. The specialty working group would welcome comments from members in Scotland and North Yorkshire where Read codes are already in use."

News of British cardiology

The seventh survey of staffing in cardiology appears in this issue. Members will note that between 1990 and 1991 no improvement occurred in the number of district hospitals without cardiologists. We have too few senior registrars, partly because of the inappropriate top slice taken for research. By the time this newsletter appears we shall have had our review with the Joint Planning Advisory Committee (JPAC). This was brought forward at our request. We believe we have an excellent case for an increase in the number of senior registrars. The Manpower and Planning Committee of the British Cardiac Society would like to know of cardiac centres that could offer facilities for additional trainees at this level. The committee could do little more than offer advice on the steps to be taken in any application. This may be helpful, however, because the procedure is complex and lengthy. An increase in allocation nationally does not guarantee manpower approval, educational approval, or funding. The delay from an application to the Joint Committee on Higher Medical Training to physician in post is likely to be at least two years.

News of the British Cardiac Society

At its recent meeting, Council discussed the attitude of the society to commercial sponsorship. Up to the present we have had little liaison with the pharmaceutical industry apart from our annual exhibition. This attitude may be too rigid. We shall explore very cautiously the possibility of closer links. Commercial sponsorship may be appropriate to help us with the refurbishment of our new premises. We should not automatically refuse to endorse meetings that have attracted some commercial sponsorship. The possibility has also been raised of joint workshops with clinical pharmacologists from industry. Council believed, however, that sponsorship for activities at our annual meeting would not be appropriate. Council was reminded that the Medical Practice Committee had a remit to support a limited number of research projects, particularly pilot studies that might be needed before major grant applications, but no applications had been received recently. A decision was taken that the society will also make available £2000 in the forthcoming 12 months to give part-support for colleagues from Eastern Europe or the third world who wish to come to cardiac meetings in Britain. Concern was expressed that entrants for the Young Research Workers Prize had no presentation at our meeting if they were not finalists—though some unsuccessful applicants had submitted excellent work. The programme committee has now decided that entrants should be encouraged to submit their abstracts for selection and presentation in the usual way.

Liam Penny has taken an initiative and brought it to the notice of Council. He has written as follows: "The Department of Health recommends that doctors with clinical contact should be immunised against hepatitis B. This is obviously particularly relevant for catheterising cardiologists. Our informal soundings suggest all too often that cardiologists are 'too busy' to protect themselves, however keen they may be to screen their patients. We suggest it may be interesting and helpful to carry out an audit of hepatitis screening policies and immunisation rates among British cardiologists (registrars, senior registrars, and consultants)." Council gave its support to this exercise which will involve a postal questionnaire, and urged colleagues and their junior staff to return the form as promptly and as accurately as they do for other British Cardiac Society questionnaires. You will be hearing from Cardiff.

Council's confidence in the British Cardiac Society surveys is not entirely inappropriate. The surveys are successful, and we always achieve a complete return eventually . . . The information is of the greatest importance and the forthcoming JPAC review underlines our need for sound data. But we are concerned that the recent facilities survey is causing unusual problems. We may have made a tactical error in suggesting that much of the questionnaire could be completed by a chief technician or a senior technician. A total of 314 forms were sent out, but 86 (27%) have not been returned despite reminder letters. We will persevere, but the extra effort we have to make is time consuming and expensive. It detracts from other activities. Cardiologists in several Regions are urging us to provide an analysis of the data which they need to support their claims for better provision locally. Without cooperation from all we cannot supply what is needed nor publish the results. We hope all our District contacts will ensure that a prompt response is made to our next reminder letter.

Peter Mills, associate editor of the *British*

Heart Journal has written the following on the subject of reports relating to British cardiology: "The British Cardiac Society and the *British Heart Journal* have agreed guidelines for the drafting and submission of reports. The aims of these guidelines are to coordinate subjects and authors and avoid duplication of effort. Reports bearing the authority of the British Cardiac Society, which will include those of its affiliated groups, should be seen by the Publications Committee before coming to the *British Heart Journal*." The guidelines, which will minimise delays, can be obtained from Peter Mills at the journal office.

News from Europe

Philip Poole-Wilson writes: "The Barcelona Congress this year is over and was judged to be a great success. The number of registrations (over 13 000) was yet another record. Over 10 000 were active participants. The continuing growth in the size of the meeting clearly indicates popularity, but does present difficulties to the European Society of Cardiology with regard to organisation and finding suitable sites. Size is not the most important measure of the success of a congress. Many of you have commented that the standard of the scientific work is still increasing. Many important studies from Europe and the world were presented. Presentations on thrombolysis and drug intervention after myocardial infarction undoubtedly will have the greatest immediate impact on medicine. In the medium to long term the sessions on genetics, molecular biology, regression of atheroma, and ischaemic syndromes may provide a basis for major therapeutic advances.

During the General Assembly a new Board for the European Society of Cardiology was elected. Michel Bertrand (France) takes over as the new President for the period 1992–4. Philip Poole-Wilson (UK) was elected President-elect, Günter Breithardt (Germany) is Secretary, Marten Simmoons (Netherlands) is Treasurer, Joan Cosin Aguilar (Spain) and Julius Papp (Hungary) are the Vice-Presidents, and Sergio Chercia (Italy), Franz Dienstl (Austria), John Gialafos (Greece), and Lars Rydén (Sweden) are the new Councillors. Five new countries have become members of the European Society of Cardiology. These are Latvia, Lithuania, Estonia, Croatia, and Slovenia. A new Working Group on Cardiovascular Surgery was created and I do hope that members of the British Cardiac Society will join it. The Working Group on Nuclear Cardiology changes its name to Nuclear Cardiology and Magnetic Resonance. The Working group on Pathophysiology of the Cardiac Myocyte changed its name to Cellular Biology of the Heart. Sixty nine new Fellows of the European Society of Cardiology (FESC) were created. Forty seven were present. These included the following from the UK: John Cleland, Christopher Davidson, Simon Joseph, Bruce Keogh, and Richard Vincent.

News of colleagues

Mark de Belder and James Hall have been appointed as consultant cardiologists to the new cardiac centre at South Cleveland Hospital; Anthony Gershlick has left his senior lecturer post to become a consultant cardiologist at the same hospital at Groby Road Leicester; Gordon Dalzell has left the Altnagelvin Hospitals in Northern Ireland to take a post at the Royal Victoria Hospital, and has been replaced by Albert McNeill. These posts attracted a total of 23 applicants — an unusually large number in these days of relative scarcity of senior registrars. Sadly, however, another appointment to a district hospital could not be made because none of the applicants was considered to be suitable for short listing. We understand the post will be re-advertised.

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